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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Shigeki SATOH et al.
SERIAL NO.: NEW U.S. PCT APPLICATION
FILED: HEREWITH
INTERNATIONAL APPLICATION NO.: PCT/JP02/13754
INTERNATIONAL FILING DATE: December 27, 2002
FOR: CYCLIC TETRAPEPTIDE COMPOUND AND USE THEREOF

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Commissioner for Patents
Alexandria, Virginia 22313

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

COUNTRY	APPLICATION NO	DAY/MONTH/YEAR
Australia	PR 9779	28 December 2001
Australia	2002952117	10 October 2002

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. PCT/JP02/13754. Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

Respectfully submitted,
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Patent Office
Canberra

I, JONNE YABSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PR 9779 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 28 December 2001.

WITNESS my hand this
Eighteenth day of November 2002

J R Yabsley

JONNE YABSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

COMMONWEALTH OF AUSTRALIA
AUSTRALIA
PATENT OFFICE

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION
for the invention entitled:

"Cyclic tetrapeptide compound and use thereof"

The invention is described in the following statement:

DESCRIPTION

CYCLIC TETRAPEPTIDE COMPOUND AND USE THEREOF

TECHNICAL FIELD

The present invention relates to a cyclic tetrapeptide compound which is useful as a medicament, to a process for producing the same and to a pharmaceutical composition comprising the same.

BACKGROUND ART

Histone deacetylases are known to play an essential role in the transcriptional machinery for regulating gene expression, and histone deacetylase inhibitors induce histone hyperacetylation and affect the gene expression. Therefore, a histone deacetylase inhibitor is useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infection, and the like.

In this connection, a cyclic tetrapeptide compound that can be used as an antitumor agent is disclosed in JP-A-7-196686 but this publication is silent on the action against histone deacetylases and the effect against the above-mentioned various diseases.

DISCLOSURE OF THE INVENTION

The present invention relates to a novel cyclic tetrapeptide compound which is useful as a medicament, to a process for producing the same and to a pharmaceutical composition comprising the same.

More particularly, it relates to a cyclic tetrapeptide compound which has a potent inhibitory effect on the activity of histone deacetylase.

The inventors of the present invention also found that a histone deacetylase inhibitor, such as cyclic tetrapeptide compound of formula (I) (hereinafter cyclic tetrapeptide compound [I] or compound [I]), has a potent immunosuppressive effect and potent antitumor effect. Therefore, a histone deacetylase inhibitor, such as cyclic tetrapeptide compound [I], is useful as an active ingredient of an immunosuppressant and an antitumor

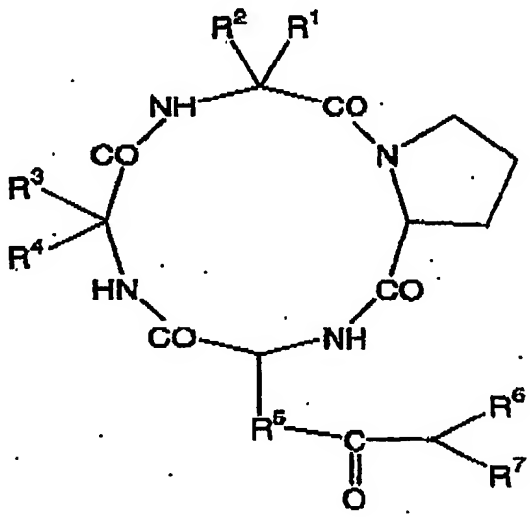
agent and useful as a therapeutic or prophylactic agent for an organ transplant rejection, autoimmune diseases, tumor, and the like.

Accordingly, one object of the present invention is to provide a compound which has biological activities as stated above.

A further object of the present invention is to provide a pharmaceutical composition containing, as an active ingredient, the cyclic tetrapeptide compound [I].

A yet further object of the present invention is to provide a use of the histone deacetylase inhibitors, such as cyclic tetrapeptide compound [I], for treating and preventing diseases stated above.

Thus, the present invention provides a cyclic tetrapeptide compound of the formula (I):



(I)

wherein
R^1 is hydrogen,
R^2 is ar(lower)alkyl optionally substituted with one or more suitable substituent(s),
R^3 and R^4 are each hydrogen or lower alkyl, or
R^3 and R^4 are linked together to form lower alkylene,
R^5 is lower alkylene or lower alkenylene,
R^6 is hydroxy or protected hydroxy, and
R^7 is lower alkyl,
providing that,
when R^3 is methyl, R^4 is methyl or ethyl, R^5 is pentylene, R^6 is

hydroxy and R^7 is methyl, then R^2 is phenyl(lower)alkyl substituted with one or more suitable substituent(s), or a salt thereof.

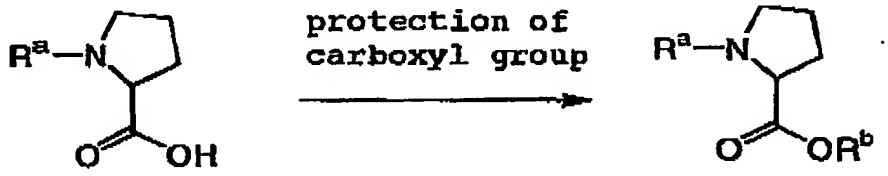
The compound [I] and a salt thereof can be prepared by the process as illustrated in the following reaction schemes.

The compound [I] of the present invention may be prepared by a liquid phase method (i.e. Preparation A → Preparation C → Examples) or a solid-liquid phase relay method (i.e. Preparation B → Preparation C → Examples).

Hereinafter, the processes for preparing the compound [I] of the present invention are explained in detail.

Preparation A

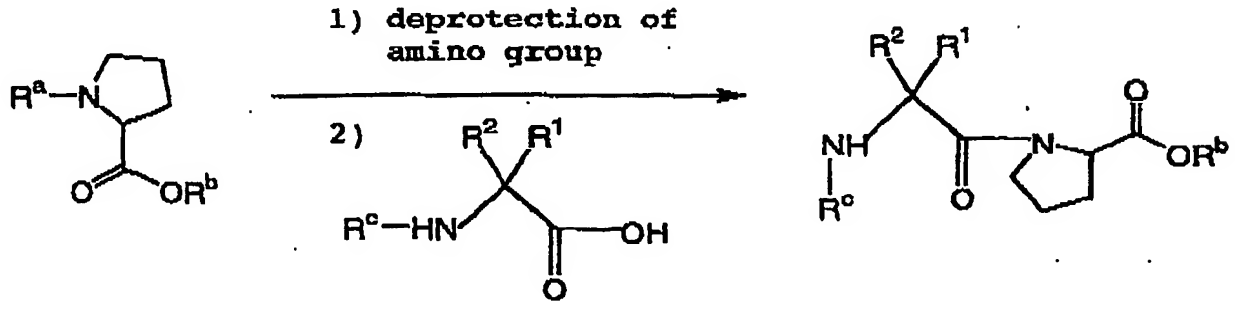
Preparation A-1



(a-1)
or a salt thereof

(a-2)
or a salt thereof

Preparation A-2

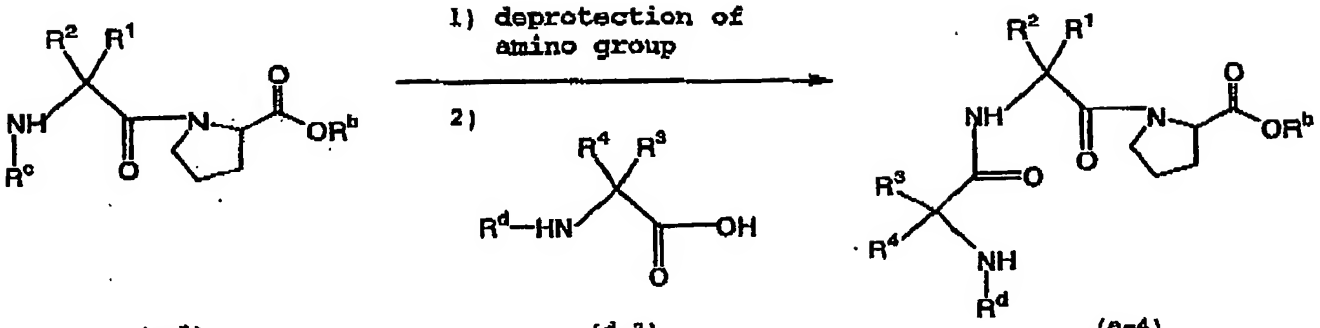


(a-2)
or a salt thereof

(d-1)
or a salt thereof

(a-3)
or a salt thereof

Preparation A-3

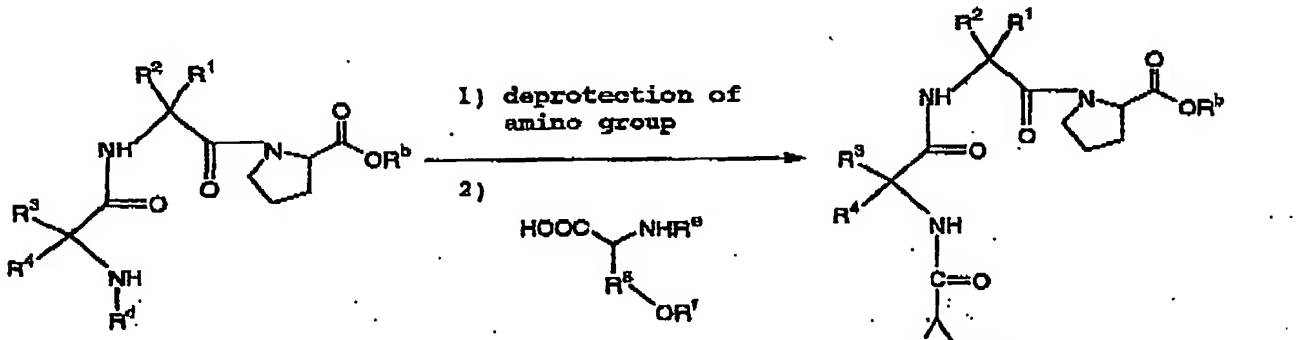


(a-3) or a salt thereof

(d-2) or a salt thereof

(a-4) or a salt thereof

Preparation A-4

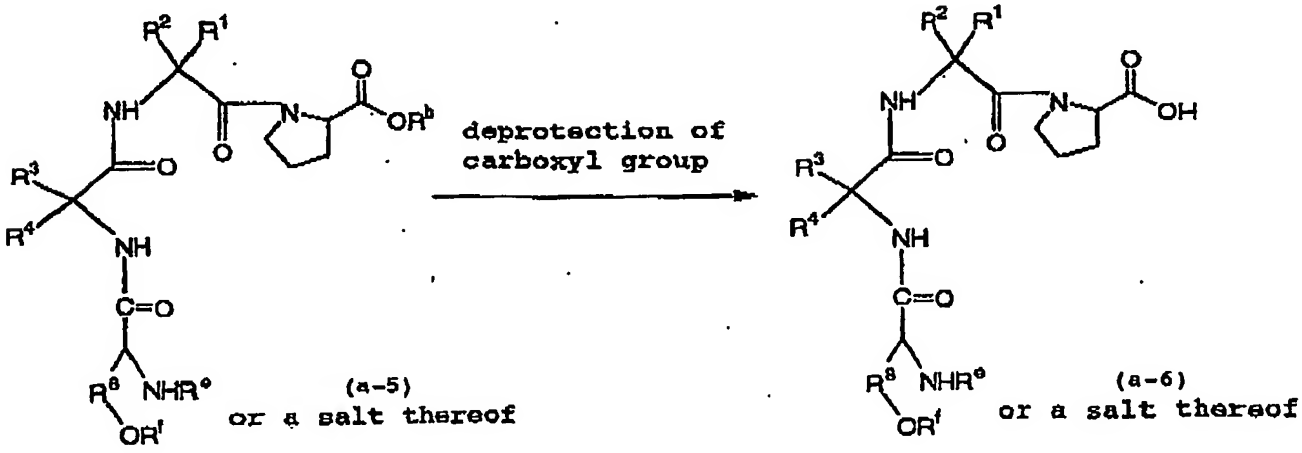


(a-4) or a salt thereof

(d-3) or a salt thereof

(a-5) or a salt thereof

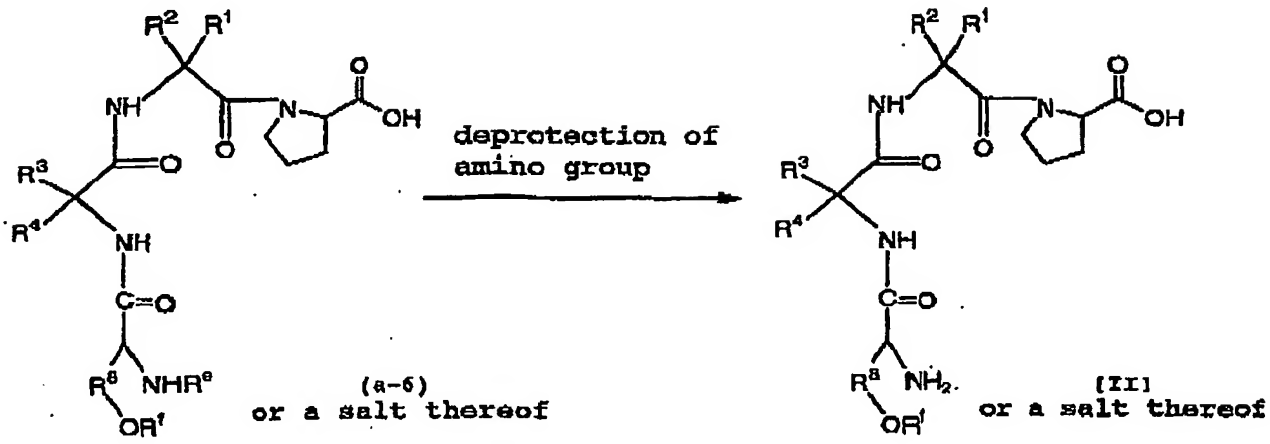
Preparation A-5



(a-5) or a salt thereof

(a-6) or a salt thereof

Preparation A-6



(a-6)
or a salt thereof

(II)
or a salt thereof

wherein

R^1, R^2, R^3 and R^4 are as defined above,

R^8 is lower alkylene,

R^a is hydrogen or amino protective group,

R^b is carboxy protective group,

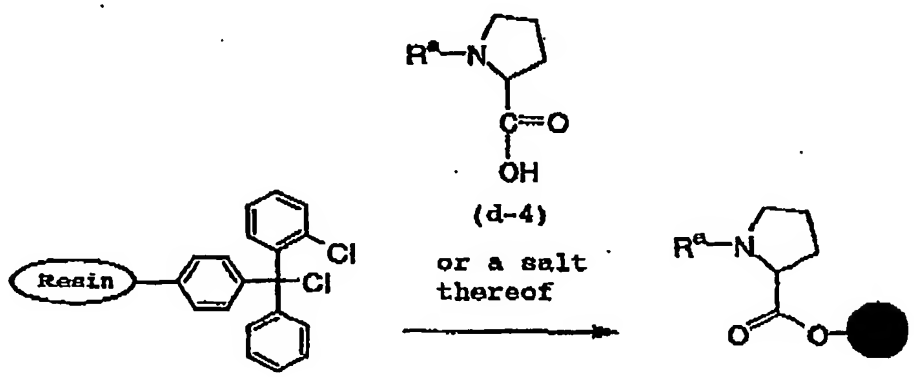
R^c, R^d and R^e are each amino protective group, and

R^f is hydroxy protective group.

In the above Preparation A, deprotection of carboxyl group (Preparation A-5) and deprotection of amino group (Preparation A-6) may be conducted simultaneously (e.g. Preparation A7-5+6, Preparation A10-5+6 and the like).

Preparation B

Preparation B-1

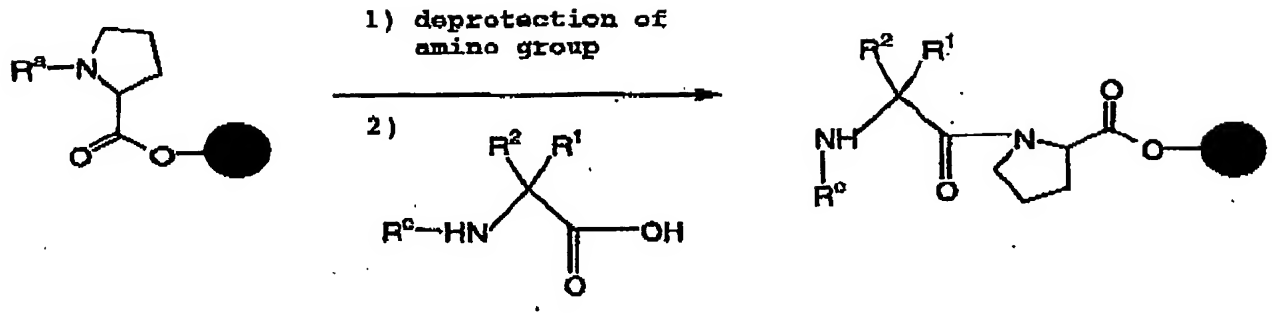


(d-4)

(b-1)
or a salt thereof

(b-2)
or a salt thereof

Preparation B-2

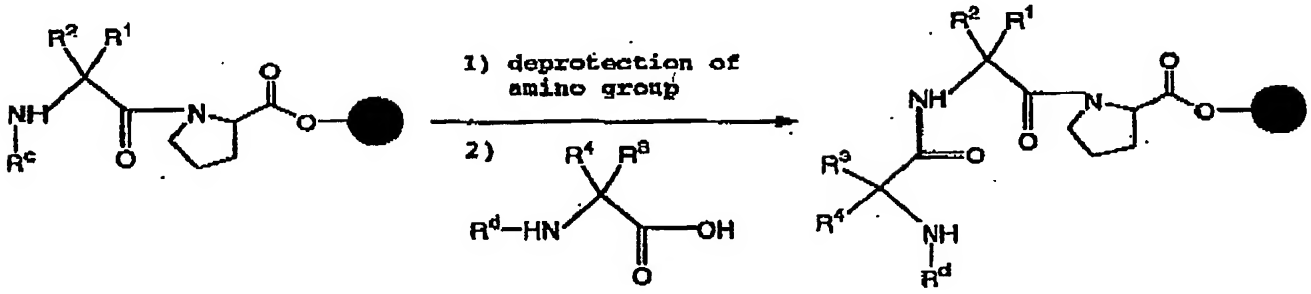


(b-2) or a salt thereof

(d-1) or a salt thereof

(b-3) or a salt thereof

Preparation B-3

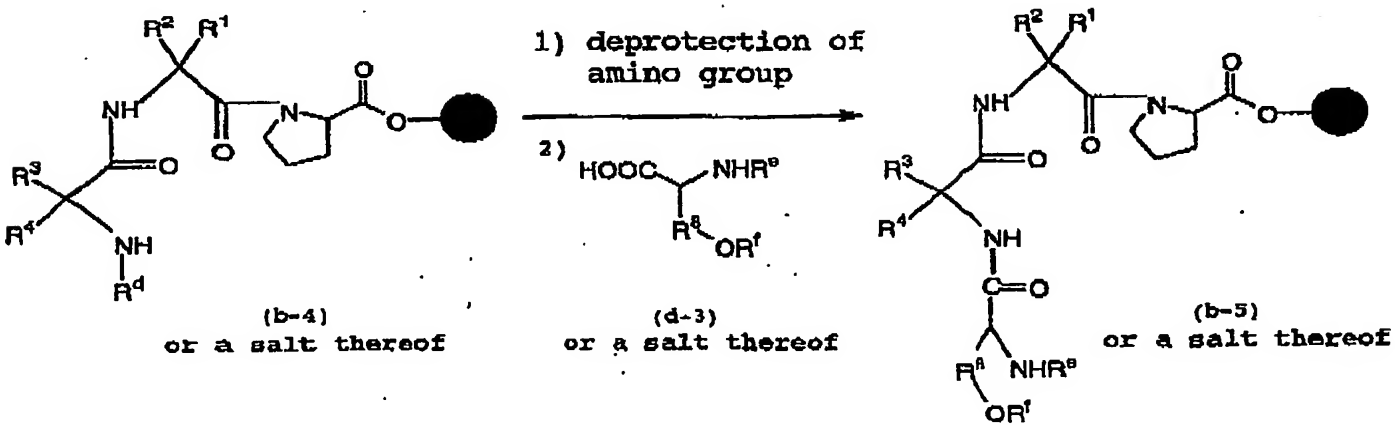


(b-3) or a salt thereof

(d-2) or a salt thereof

(b-4) or a salt thereof

Preparation B-4

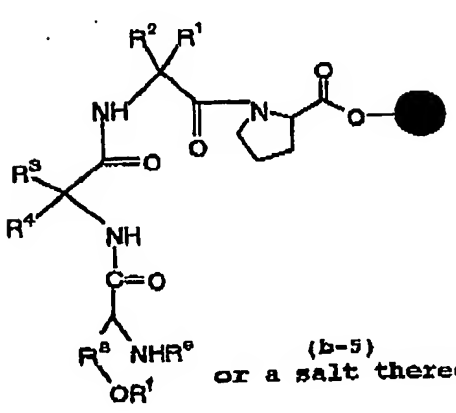


(b-4) or a salt thereof

(d-3) or a salt thereof

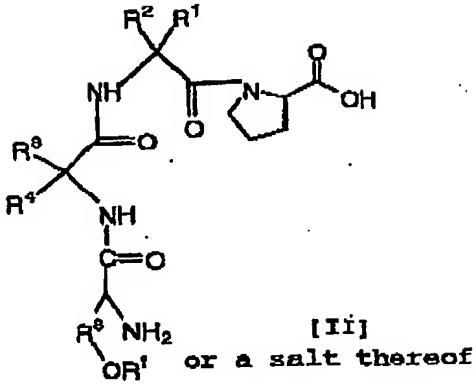
(b-5) or a salt thereof

Preparation B-5



(b-5)
or a salt thereof

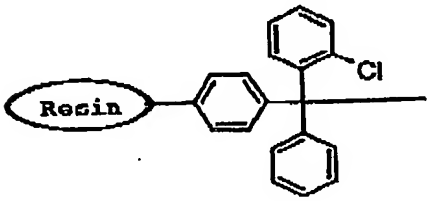
deprotection of amino group and carboxyl group attached to the resin unit



[II]
or a salt thereof

wherein
R^1, R^2, R^3 and R^4 are as defined above,
R^6 is lower alkylene,
R^a is hydrogen or amino protective group,
R^c, R^d and R^e are each amino protective group,
R^f is hydroxy protective group, and

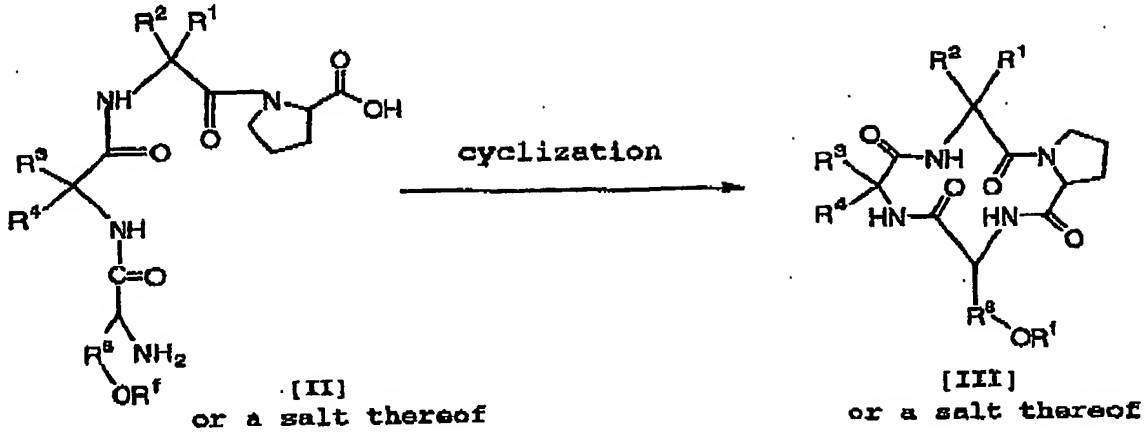
● is the following resin unit:



wherein (Resin) is a resin.

Preparation C

Preparation C-1



[II]
or a salt thereof

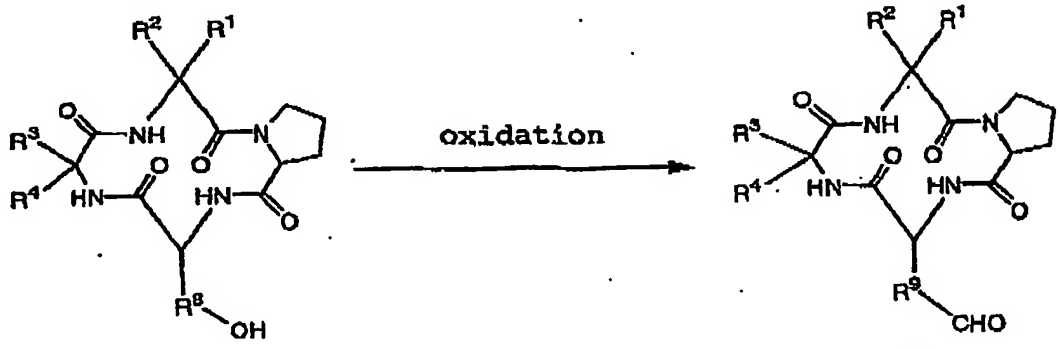
[III]
or a salt thereof

Preparation C-2

[III]
or a salt thereof

[IV]
or a salt thereof

Preparation C-3



[IV]
or a salt thereof

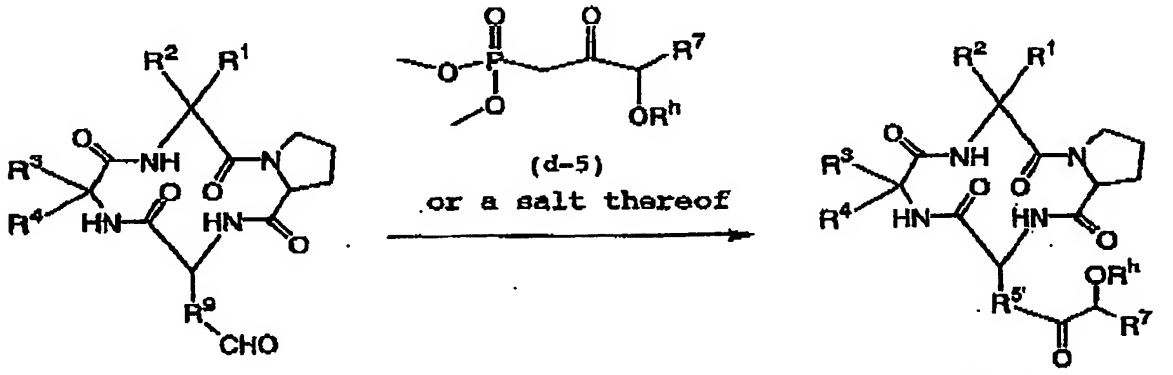
[V]
or a salt thereof

wherein
R^1, R^2, R^3 and R^4 are as defined above,
R^8 and R^9 are each lower alkylene, and
R^f is a hydroxy protective group.

The compound [V] obtained from the Preparation C is used in the next preparation, i.e. Preparation I-1 to I-3 to give the compounds [I-1], [I-2] and [I-3]. All of these compounds are included in the scope of the compound [I] of the present invention.

Preparation of the compound [I] of the present invention

Preparation of the compound [I-1]

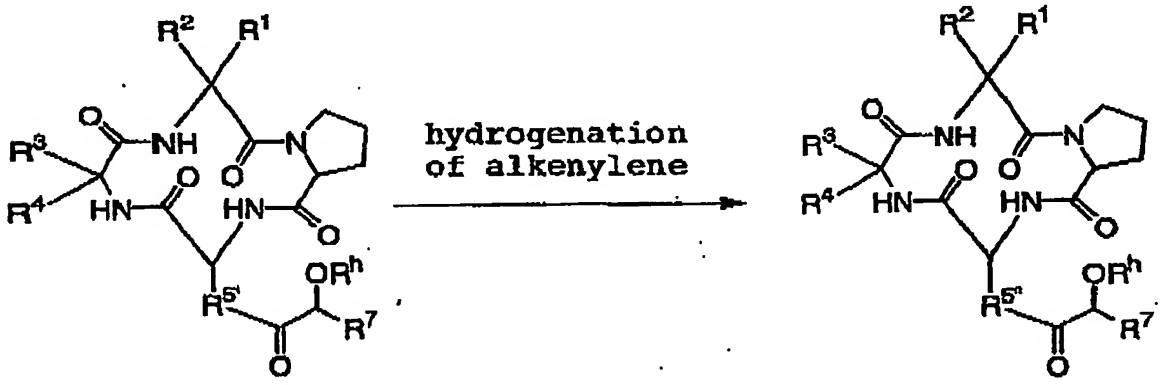


[V]
or a salt thereof

(d-5)
or a salt thereof

[I-1]
or a salt thereof

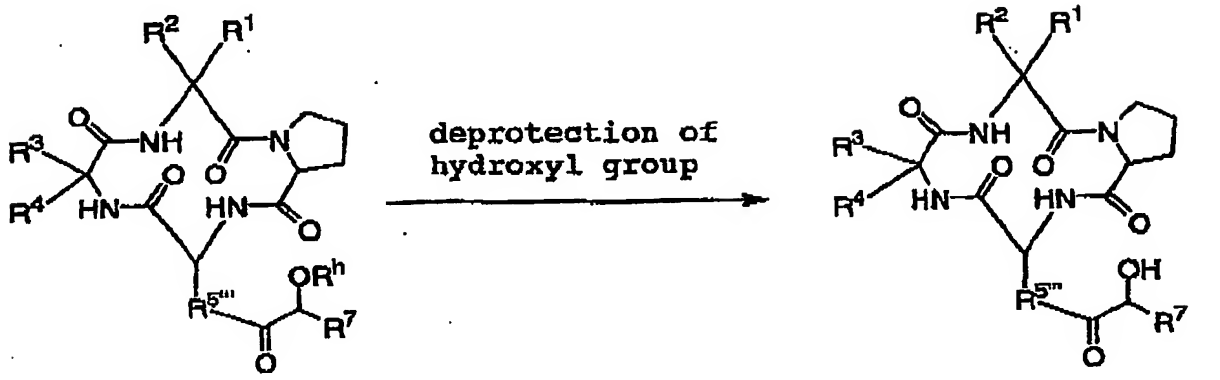
Preparation of the compound [I-2]



[I-1]
or a salt thereof

[I-2]
or a salt thereof

Preparation of the compound [I-3]



[I-1] or [I-2]
or a salt thereof

[I-3]
or a salt thereof

wherein
R^1, R^2, R^3, R^4, R^7 and R^9 are as defined above,
$R^{5'}$ is lower alkenylene,
$R^{5''}$ is lower alkylene,
$R^{5'''}$ is lower alkylene or lower alkenylene, and
R^h is hydroxy protective group.

To determine absolute configuration of the hydroxyl group of the compound [I-3] and to estimate optical purity of the isomer of the compound [I-3], the compound [I-3] is reacted with a reagent such as (R or S)-(+ or -)-α-methoxy-α-trifluoromethyl-α-phenylacetyl chloride, 1-naphthylmethoxyacetic acid, 2-naphthylmethoxyacetic acid, 9-anthrylmethoxyacetic acid, 2-anthrylmethoxyacetic acid, and the like. This reaction is exemplified by Example 10-4.

Suitable "salt" is a pharmaceutically acceptable and conventional non-toxic salt, and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkaline metal salt (e.g., sodium salt, potassium salt, and the like), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, and the like), an ammonium salt;
a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, diisopropylethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, and the like);

an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, and the like);
an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, and the like); and
a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, and the like).

Suitable examples and illustration of the various definitions in the above and subsequent descriptions, which the present invention intends to include within the scope thereof, are explained in detail as follows:

The term "halogen" means fluorine, chlorine, bromine, and iodine.

The term "lower" used in the description is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable example of "one or more" may be the number of 1 to 6, preferably 1 to 3.

Suitable example of "lower alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neopentyl, hexyl, isohexyl and the like, in which the preferred one for R^3 and R^4 may be methyl, ethyl, propyl and t-butyl.

Suitable example of "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene and the like. The preferred lower alkylene for R^3 and R^4 may be tetramethylene, and the preferred one for R^5 may be pentamethylene.

Suitable example of "lower alkenylene" may include straight or branched one having 1 to 6 carbon atom(s), such as ethenylene, 1-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, 1-hexenylene, 2-hexenylene, 3-hexenylene, 4-hexenylene, 5-hexenylene and the like, in which the preferred one for R^5 may be 1-pentenylene.

Suitable example of ar(lower)alkyl may include phenyl(lower)alkyl [e.g. phenyl(C_1-C_6)alkyl such as benzyl, phenetyl, phenylpropyl, phenylbutyl, phenylhexyl and the like],

and the like. The preferred one for R^2 may be phenyl(C_1-C_6)alkyl, more preferably benzyl.

Suitable example of "suitable substituent(s)" for R^2 may include lower alkoxy, ar(lower)alkyloxy, cyano, hydroxy, halogen, and the like.

Suitable carboxy protective group may include:
lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl and the like), preferably methyl, ethyl and t-butyl;
mono(or di or tri)halo(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl and the like), preferably 2,2,2-trichloroethyl;
lower alkanoyloxy(lower)alkyl (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, hexanoyloxymethyl, 1(or 2)-acetoxyethyl, 1(or 2 or 3)-acetoxypropyl, 1(or 2 or 3 or 4)-acetoxybutyl, 1(or 2)-propionyloxyethyl, 1(or 2 or 3)-propionyloxypropyl, 1(or 2)-butyryloxyethyl, 1(or 2)-isobutyryloxyethyl, 1(or 2)-pivaloyloxyethyl, 1(or 2)-hexanoyloxyethyl, isobutyryloxymethyl, 2-ethylbutyryloxymethyl, 3,3-dimethylbutyryloxymethyl, 1(or 2)-pentanoyloxyethyl, and the like);
lower alkanesulfonyl(lower)alkyl (e.g. 2-mesylethyl and the like);
lower alkoxycarbonyloxy(lower)alkyl (e.g. methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, 2-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl, and the like);
[5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl](lower)alkyl (e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-propyl-2-oxo-1,3-dioxol-4-yl)methyl, and the like);
aryl optionally substituted with one or more suitable substituent(s) (e.g. phenyl, o(or m or p)-chlorophenyl, tolyl, o(or m or p)-t-butylphenyl, xylyl, mesityl, cumenyl, and the like);
ar(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyl, p-methoxybenzyl, o(or p)-nitrobenzyl, phenethyl, trityl, benzhydryl, bis(methoxyphenyl)methyl, m,p-dimethoxybenzyl, 4-hydroxy-3,5-di-t-butylbenzyl, and the like), preferably benzyl, p-methoxybenzyl and o(or p)-nitrobenzyl;

arylcarbonyl(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. phenacyl and the like);
cyclo(lower)alkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like);
lower alkenyl (e.g. vinyl, allyl, and the like), preferably allyl;
lower alkynyl (e.g. ethynyl, propynyl, and the like);
trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl, and the like), lower alkyldiarylsilyl (e.g. methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl, and the like), and the like, preferably trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl and tert-butyldiphenylsilyl;
tri(lower)alkylsilyl(lower)alkyl (e.g. 2-(trimethylsilyl)ethyl and the like);
1-(lower)alkyl-2,6,7-trioxabicyclo[2.2.2]oct-4-yl (e.g. 1-methyl-2,6,7-trioxabicyclo[2.2.2]oct-4-yl, 1-ethyl-2,6,7-trioxabicyclo[2.2.2]oct-4-yl, and the like); and the like.

Suitable hydroxy protective group may include:
lower alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, and the like, preferably methyl;
lower alkoxy(lower)alkyl (e.g. methoxymethyl and the like);
lower alkoxy(lower)alkoxy(lower)alkyl (e.g. 2-methoxyethoxymethyl and the like);
ar(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyl, p-methoxybenzyl, m,p-dimethoxybenzyl, and the like), preferably benzyl;
ar(lower)alkoxy(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyloxymethyl, p-methoxybenzyloxymethyl, and the like);
(lower)alkylthio(lower)alkyl (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, and the like), and the like, preferably methylthiomethyl;
trisubstituted silyl such as tri(lower)alkylsilyl (e.g.

trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl, and the like), lower alkyldiarylsilyl (e.g. methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl, and the like), and the like, preferably tert-butyldimethylsilyl and tert-butyldiphenylsilyl;
acyl as described below [e.g. aliphatic acyl such as lower alkanoyl (e.g. acetyl, propanoyl, pivaloyl, and the like); aromatic acyl (e.g. benzoyl, toluoyl, naphthoyl, fluorenylcarbonyl and the like);
lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, and the like), and the like;
ar(lower)alkoxycarbonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyloxycarbonyl, bromobenzyloxycarbonyl and the like);
lower alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, and the like);
lower alkoxysulfonyl (e.g. methoxysulfonyl, ethoxysulfonyl, and the like);
ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, naphthylisobutanoyl, naphthylpentanoyl, naphthylhexanoyl, and the like);
ar(lower)alkenoyl such as ar(C_3-C_6)alkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, naphthylpropenoyl, naphthylbutenoyl, naphthylmethacryloyl, naphthylpentenoyl, naphthylhexenoyl, and the like); and the like];
lower alkenyl (e.g. vinyl, allyl, and the like), preferably allyl;
tetrahydropyranyl; and the like.

Suitable "amino protective group" may include:
acyl as exemplified for the hydroxy protective group;
ar(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyl, p-methoxybenzyl, o(or p)-nitrobenzyl, phenethyl, trityl,

benzhydryl, bis(methoxyphenyl)methyl, m,p-dimethoxybenzyl, 4-hydroxy-3,5-di-t-butylbenzyl, and the like);
[5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl](lower)alkyl (e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-propyl-2-oxo-1,3-dioxol-4-yl)methyl, and the like), and the like; and the like.

Suitable "acyl" for the present invention may be illustrated as follows:

aliphatic acyl such as alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, pivaloyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, and the like);

alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, heptyloxycarbonyl, and the like);

alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, and the like);

alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, and the like); and the like;

aromatic acyl such as aroyl (e.g., benzoyl, toluoyl, naphthoyl, fluorenylcarbonyl, and the like);

ar(lower)alkanoyl such as phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, and the like), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, and the like), and the like;

ar(lower)alkenoyl such as ar(C_3-C_6)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, and the like), naphthyl(C_3-C_6)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, naphthylmethacryloyl, naphthylpentenoyl, naphthylhexenoyl, and the like), and the like;

ar(lower)alkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, and the like), fluorenyl(lower)alkoxycarbonyl (e.g., fluorenylmethyloxycarbonyl, and the like), and the like;

aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, and

the like);
aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, and the like);
arylcarbamoyl (e.g., phenylcarbamoyl and the like);
arylthiocarbamoyl (e.g., phenylthiocarbamoyl and the like);
arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, and the like);
arylsulfonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g., phenylsulfonyl, p-tolylsulfonyl, and the like);
heterocyclic acyl (e.g. heterocycliccarbonyl and the like);
heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, and the like);
heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, and the like); heterocyclicglyoxyloyl; and the like.

Suitable "heterocyclic" moiety in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkanoyl", heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" may be a moiety containing one or more hetero ring(s) having at least one heteroatom selected from sulfur atom, oxygen atom and nitrogen atom.

Any "resin" known in the field of peptide synthesis may be used for the synthesis of the compound [I] of the present invention. Suitable example of the "resin" for the synthesis of the compound [I] includes 2-chlorotrityl resin and the like.

When the compound [I] has stereoisomers, such isomers are also encompassed in the present invention.

The compound [I] may form a salt, which is also encompassed in the present invention. For example, when a basic group such as an amino group is present in a molecule, the salt is exemplified by an acid addition salt (e.g. salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, and the like, salt with an organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, salicylic acid, and the like) is exemplified, and when an acidic group such as carboxyl group is present, a basic salt (e.g. salt with a metal such as sodium, potassium, calcium, magnesium, aluminium,

and the like, a salt with amino acid such as lysine, and the like), and the like.

In addition, solvates of the compound [I] such as hydrate, ethanolate, and the like, are also encompassed in the present invention.

Hereinafter the reactions in each Preparations and Examples for preparing the cyclic tetrapeptide compound [I] of the present invention are explained in more detail. The invention should not be restricted by the following Preparations and Examples in any way.

Preparation A

Preparation A-1

The compound (a-2) can be prepared by protecting the carboxyl group of the compound (a-1).

Suitable protective agent for the reaction may be, for example, benzylhalide (e.g. benzylbromide and the like), methyl iodide, ethyl iodide, substituted benzyl halide, and the like.

The reaction may be carried out in the presence of a base (e.g. cesium carbonate, potassium carbonate, sodium carbonate, sodium hydrogen carbonate, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, and the like).

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. N,N-dimethylformamide, N-methylpyrrolidone, tetrahydrofuran, dimethylsulfoxide, and the like).

The reaction temperature is not critical and the reaction is usually carried out from under cooling to heating.

This Preparation is exemplified by Preparation A1-1 and the like.

Preparation A-2

The compound (a-3) can be prepared by 1) deprotecting the amino group of the compound (a-2) and 2) reacting the compound (a-2) with the compound (d-1).

1)Deprotection of the amino group of the compound (a-2)

Suitable deprotective agent for the reaction may be, for example, hydrogen chloride in suitable solvents (such as ethyl acetate, 1,4-dioxane, methanol, ethanol, and the like), trifluoroacetic acid, N,N-diethylamine, and the like. The deprotection may also be conducted with a hydrogenolysis catalyst

(e.g. palladium on carbon (Pd-C), palladium hydroxide on carbon, and the like) under hydrogen atmosphere. Specifically, when the carboxyl protective group of the compound (a-2) is t-butyl (e.g. Compound A7-1) and the like, the reaction is carried out in the presence of the above-mentioned hydrogenolysis catalyst under hydrogen atmosphere.

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. ethyl acetate, dioxane, dichloromethane, acetonitrile, methanol, ethanol, tetrahydrofuran, acetic acid, and the like). Specifically, when trifluoroacetic acid is used as a deprotective agent, the reaction is generally carried out in dichloromethane or without solvent (neat).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating under the pressure of 1-5 atm.

Alternatively, the compound (a-2) in which the amino group is not protected, may be obtained by directly protecting the carboxyl group of D-proline, in substantially the same manner as Preparation A-1.

2) Reaction of the compound (a-2) with the compound (d-1)

The reaction may be carried out in the presence of carbodiimide [e.g. 1-ethyl-3-(3'-N,N-dimethylaminopropyl)-carbodiimide (EDC) or hydrochrolide thereof, dicyclohexylcarbodiimide (DCC), and the like], benzotriazol-1-yloxy-tris-pyrrolidinophosphonium hexafluorophosphate (PyBOP®), benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluoro phosphate (BOP), bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBroP®), 1,1'-carbonyldiimidazol (CDI), diphenylphosphoryl azide (DPPA), 1-hydroxybenzotriazole (HOBT), benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium-hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluromium tetrafluoroborate (TBTU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), and the like, and a base [e.g. Hünig base (e.g. N,N-diisopropylethylamine, triethylamine, and the like), and the like], and the like.

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g.

dichloromethane, N,N-dimethylformamide, and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Preparation is exemplified by Preparation A1-2 and the like.

Preparation A-3

The compound (a-4) can be prepared by 1) deprotecting the amino group of the compound (a-3) and 2) reacting the compound (a-3) with the compound (d-2).

1) Deprotection of the amino group of the compound (a-3)

The reaction may be carried out in substantially the same manner as described above for the deprotection of the amino group of the compound (a-2) in the Preparation A-2. Specifically, when the amino protective group is fluorenylmethyloxycarbonyl (Fmoc) and the deprotecting agent is N,N-diethylamine, the reaction is generally carried out in a solvent such as N,N-dimethylformamide, acetonitrile, dichloromethane, and the like, or without solvent (neat).

2) Reaction of the compound (a-3) with the compound (d-2)

The reaction may be carried out in substantially the same manner as described above for the reaction of the compound (a-2) with the compound (d-1) in the Preparation A-2.

This Preparation is exemplified by Preparation A1-3 and the like.

Preparation A-4

The compound (a-5) can be prepared by 1) deprotecting the amino group of the compound (a-4) and 2) reacting the compound (a-4) with the compound (d-3).

1) Deprotection of the amino group of the compound (a-4)

The reaction may be carried out in substantially the same manner as described above for the deprotection of the amino group of the compound (a-2) in the Preparation A-2.

2) Reaction of the compound (a-4) with the compound (d-3)

This reaction may be carried out in substantially the same manner as described above for the reaction of the compound (a-2) with the compound (d-1) in the Preparation A-2.

This Preparation is exemplified by Preparation A1-4 and the like.

Preparation A-5

The compound (a-6) can be prepared by deprotecting the carboxyl group of the compound (a-5).

The reaction may be carried out using a catalyst (e.g. Pearlman catalyst ($Pd(OH)_2$-C), palladium on carbon (Pd-C), and the like) under hydrogen atmosphere. The reaction may also be carried out using an alkali (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like).

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. methanol, ethanol, ethyl acetate, 1,4-dioxane, tetrahydrofuran, and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This reaction is exemplified by Preparation A1-5 and the like.

Preparation A-6

The compound [II] may be prepared by deprotecting the amino group of the compound (a-6).

The reaction may be carried out in substantially the same manner as described for the deprotection of the amino group of the compound (a-2) in the Preparation A-2.

This Preparation is exemplified by Preparation A1-6 and the like.

Preparation A-5+6

Alternatively, when the carboxy protective group is t-butyl, the deprotection of carboxyl group and amino group of the compound (a-5) may be conducted simultaneously to give the compound [II].

In this case, suitable deprotective agent for this reaction may be, for example, trifluoroacetic acid and the like.

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. dichloromethane, and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This reaction is exemplified by Preparation A7-5+6, A10-5+6, and the like.

The compound [II] as obtained above is used in the Preparation C.

Preparation B

Preparation B-1

The compound (b-2) may be prepared by reacting the compound (b-1) with the compound (d-4).

The reaction may be carried out in the presence of a base (e.g. diisopropylethylamine) in suitable solvent (e.g. dichloromethane, ethyl acetate, 1,4-dioxane, methanol, ethanol, and the like).

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. dichloromethane and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Preparation is exemplified by Preparation B1-1 and the like.

Preparation B-2

The compound (b-3) may be prepared by 1) deprotecting the amino group of the compound (b-2), and 2) reacting the compound (b-2) with the compound (d-1).

1) Deprotection of the amino group of the compound (b-2)

The reaction may be carried out in substantially the same manner as described above for the deprotection of the amino group of the compound (a-2) in the Preparation A-2.

2) Reaction of the compound (b-2) with the compound (d-1)

The reaction may be carried out in the presence of PyBOP®, HATU, and the like, and a base (e.g. Hünig base (e.g. N,N-diisopropylethylamine and the like) and the like).

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. N,N-dimethylformamide and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Preparation is exemplified by Preparation B1-2 and the like.

Preparation B-3

The compound (b-4) may be prepared by 1) deprotecting the amino group of the compound (b-3), and 2) reacting the compound (b-3) with the compound (d-2).

1) Deprotection of the amino group of the compound (b-3)

The reaction may be carried out in substantially the same manner as described above for the deprotection of the amino group of the compound (a-2) in the Preparation A-2.

2) Reaction of the compound (b-3) with the compound (d-2)

The reaction may be carried out in substantially the same manner as in Preparation B-2.

This Preparation is exemplified by Preparation B1-3 and the like.

Preparation B-4

The compound (b-5) may be prepared by 1) deprotecting the amino group of the compound (b-4), and 2) reacting the compound (b-4) with the compound (d-3).

1) Deprotection of the amino group of the compound (b-4)

The reaction may be carried out in substantially the same manner as described above for the deprotection of the amino group of the compound (a-2) in the Preparation A-2.

2) Reaction of the compound (b-4) with the compound (d-3)

The reaction may be carried out in the presence of PyBOP®, HATU, and the like, and a base (e.g. Hünig base (e.g. N,N-diisopropylethylamine and the like) and the like).

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. dichloromethane, N,N-dimethylformamide, and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Preparation is exemplified by Preparation B1-4 and the like.

Preparation B-5

The compound [II] may be prepared by deprotecting the amino group and the carboxyl group attached to the resin unit of the compound (b-5).

The reaction may be carried out in the presence of an acid (e.g. trifluoroacetic acid and the like).

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. dichloromethane and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Preparation is exemplified by Preparation B1-5 and the

like.

The compound [II] is used in the Preparation C.

Preparation C

Preparation C-1

The compound [III] may be prepared by cyclizing the compound [II].

The reaction may be carried out in the presence of a reagent (e.g. HATU, BOP, PyBOP®, TBTU, HOBT, and the like), and a base (e.g. dimethylaminopyridine, triethylamine, N,N-diisopropylethylamine, and the like).

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. N,N-dimethylformamide, methylene chloride, and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Preparation is exemplified by Preparation C1-1 and the like.

Preparation C-2

The compound [IV] may be prepared by deprotecting the hydroxyl group of the compound [III].

The reaction may be carried out in the presence of a base (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium methoxide, and the like).

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. methanol, ethanol, 1,4-dioxane, tetrahydrofuran, and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Preparation is exemplified by Preparation C1-2 and the like.

Preparation C-3

The compound [V] may be prepared by oxidation of the compound [IV].

Suitable oxidizing agent in the reaction may be, for example, Dess-Martin periodinane (i.e. 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one), and the like.

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. dichloromethane, dimethylsulfoxide, and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Preparation is exemplified by Preparation C1-3 and the like.

The compound [V] is used in the Preparation of the compound [I] of the present invention.

Preparation of the compound [I] of the present invention

Preparation of the compound [I-1]

The compound [I-1] may be prepared by reacting the compound [V] with the compound (d-5).

Suitable compound (d-5) for the reaction may be, for example, dimethyl (3R)-tert-butyldimethylsilyloxy-2-oxobutylphosphonate, dimethyl (3S)-tert-butyldimethylsilyloxy-2-oxobutylphosphonate, dimethyl (3R)-tert-butyldimethylsilyloxy-2-oxoheptylphosphonate, and the like.

The reaction may be carried out in the presence of a base (e.g. barium hydroxide octahydrate, barium hydroxide monohydrate, sodium hydroxide, potassium tert-butoxide, cesium carbonate, and the like).

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. tetrahydrofuran, tetrahydrofuran-water mixture, N,N-dimethylformamide, dimethylsulfoxide, acetonitrile, ethanol, 2-propanol, and the like).

The temperature of the reaction is not critical and the reactions are usually carried out from under cooling to heating.

The reaction may also be carried out in the presence of an organic base (e.g. Hünig base, DBU, and the like) and a lithium salt (e.g. lithium chloride, lithium bromide, lithium iodide, and the like), in a suitable solvent (e.g. acetonitrile, dimethylformamide, and the like) [Horner-Wadsworth-Emmons reaction].

The temperature of the reaction is not critical and the reactions are usually carried out from under cooling to heating.

The Preparation of the compound [I-1] is exemplified by Example 1-1 and the like.

Preparation of the compound [I-2]

The compound [I-2] may be prepared by hydrogenation of alkenylene of the compound [I-1].

Suitable catalyst for the hydrogenation may be, for example, palladium-$BaSO_4$ (Pd-$BaSO_4$), palladium on carbon (Pd-C), $Pd(OH)_2$ on carbon, and the like.

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. methanol, ethyl acetate, ethanol, 1,4-dioxane, and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

The Preparation of the compound [I-2] is exemplified by Example 1-2 and the like.

Preparation of the compound [I-3]

The compound [I-3] may be prepared by deprotecting the hydroxyl group of the compound [I-1] or [I-2].

Suitable agent for the reaction may be, for example, tetrabutylammonium fluoride, pyridinium poly(hydrogen fluoride), hydrogen fluoride, cesium fluoride, potassium fluoride, and the like.

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. tetrahydrofuran, N,N-dimethylformamide, pyridine, and the like). Optionally, the reaction may be carried out in the presence of a catalyst (e.g. Pearlman catalyst ($Pd(OH)_2$-C), palladium on carbon (Pd-C), and the like) under hydrogen atmosphere.

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

The Preparation of the compound [I-3] is exemplified by Example 1-3 and the like.

To determine absolute configuration of the hydroxyl group of the compound [I-3] and to estimate optical purity of the isomer of the compound [I-3], the compound [I-3] is reacted with a reagent such as (R)-(-)-α-methoxy-α-trifluoromethyl-α-phenylacetyl chloride, (S)-(+)-α-methoxy-α-trifluoromethyl-α-phenylacetyl chloride, and the like.

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction (e.g. pyridine, methylene chloride, and the like).

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This reaction is exemplified by Example 10-4.

Test Method

In order to show the usefulness of the compound [I] of the invention, the pharmacological test result of the representative compounds of the present invention is shown in the following.

Test 1: Determination of histone deacetylase inhibitor activity

The partial purification of human histone deacetylase, the preparation of [^{3}H] acetyl histones, and the assay for histone deacetylase activity were performed basically according to the method as proposed by Yoshida et al. as follows.

Partial purification of human histone deacetylase

The human histone deacetylase was partially purified from human T cell leukemia Jurkat cells. Jurkat cells (5 X 10^8 cells) were suspended in 40 ml of the HDA buffer consisting of 15 mM potassium phosphate, pH 7.5, 5% glycerol and 0.2 mM EDTA. After homogenization, nuclei were collected by centrifugation (35,000 x g, 10 min) and homogenized in 20 ml of the same buffer supplemented with 1 M $(NH_4)_2SO_4$. The viscous homogenate was sonicated and clarified by centrifugation (35,000 x g, 10 min), and the deacetylase was precipitated by raising the concentration of $(NH_4)_2SO_4$ to 3.5 M. The precipitated protein was dissolved in 10 ml of the HDA buffer and dialyzed against 4 liters of the same buffer. The dialyzate was then loaded onto a DEAE-cellulose (Whatman DE52) column (25 x 85 mm) equilibrated with the same buffer and eluted with 300 ml of a linear gradient (0-0.6 M) of NaCl. A single peak of histone deacetylase activity appeared between 0.3 and 0.4 M NaCl.

Preparation of [^{3}H] acetyl histone

To obtain [^{3}H] acetyl-labeled histone as the substrate for the histone deacetylase assay, 1 x 10^8 cells of Jurkat in 20 ml of RPMI-1640 medium (supplemented with 10% FBS, penicillin (50 units/ml) and streptomycin (50μg/ml)) were incubated with 300 MBq [^{3}H] sodium acetate in the presence of 5 mM sodium butyrate for 30 minutes in 5% CO_2-95% air atmosphere at 37°C in a 75 cm^2 flask, harvested into a centrifuge tube (50 ml), collected by centrifugation at 1000 rpm for 10 minutes, and washed once with phosphate-buffered saline. The washed cells were suspended in 15 ml of ice-cold lysis buffer (10 mM Tris-HCl, 50 mM sodium bisulfite, 1% Triton X-100, 10 mM $MgCl_2$, 8.6% sucrose, pH 6.5). After Dounce homogenization (30 stroke), the nuclei were

collected by centrifugation at 1000 rpm for 10 minutes, washed 3 times with 15 ml of the lysis buffer, and once with 15 ml of ice-cooled washing buffer (10 mM Tris-HCl, 13 mM EDTA, pH 7.4) successively. The pellet was suspended in 6 ml of ice-cooled water using a mixer, and 68μl of H_2SO_4 was added to the suspension to give a concentration of 0.4 N. After incubation at 4°C for 1 hour, the suspension was centrifuged for 5 minutes at 15,000 rpm, and the supernatant was taken and mixed with 60 ml of acetone. After overnight incubation at -20°C, the coagulated material was collected by microcentrifugation, air-dried, and stored at -80°C.

Assay for histone deacetylase activity

For the standard assay, 10 μl of [^{3}H] acetyl-labeled histones were added to 90μl of the enzyme fraction, and the mixture was incubated at 25°C for 30 minutes. The reaction was stopped by addition of 10 μl of HCl. The released [^{3}H] acetic acid was extracted with 1 ml of ethyl acetate, and 0.9 ml of the solvent layer was taken into 10 ml of toluene scintillation solution for determination of radioactivity.

Test 2: Determination of T-cell growth inhibitor activity

The T lymphocyte blastogenesis test was performed in microtiter plates with each well containing 1.5×10^5 splenic cells of Lewis rats in 0.1 ml RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 50 mM 2-mercaptoethanol, penicilln (100 units/ml) and streptomycin (100μg/ml), to which Concanavalin A (1μg/ml) was added. The cells were incubated at 37°C in a humidified atmosphere of 5% CO_2 for 72 hours. After the culture period, suppressive activities of the test compounds in T lymphocyte blastogenesis were quantified by AlamarBlue™ Assay. The test samples were dissolved in DMSO and further diluted with RPMI-1640 medium and added to the culture. The activities of the test compounds were expressed as IC_{50}.

The results of those tests are shown in the Table 1.

Table 1: HDAC inhibitory activity and T-cell growth inhibitory activity of the compound of the present invention

Example	Test 1: HDAC inhibitory activity IC_{50} (nM)	Test 2: T-cell growth inhibitory activity IC_{50} (nM)
Compound E1-3(1)	19	19
Compound E1-3(3)	15	21
Compound E2-3(1)	12	1.0
Compound E3-3	16	15
Compound E5-3	14	2.9
Compound E6-3	15	1.1
Compound E7-3(1)	29	13
Compound E7-3(2)	200	180
Compound E7-3(3)	76	19
Compound E8-3	12	3.6
Compound E9-3	19	47
Compound E10-3(1)	2000	34
Compound E10-3(2)	74	23
Compound E10-3(3)	1000	25
Compound E11-3	34	77
Compound E12-3	860	>1000

The pharmaceutical composition of the present invention comprising histone deacetylase inhibitor, such as the compound [I], is useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infection and the like. Further, it is useful as an antitumor agent or immunosuppressant, which prevents an organ transplant rejection and autoimmune diseases as exemplified below.

Rejection reactions by transplantation of organs or tissues such as the heart, kidney, liver, bone marrow, skin, cornea, lung, pancreas, small intestine, limb, muscle, nerve, intervertebral disc, trachea, myoblast, cartilage, and the like;
graft-versus-host reactions following bone marrow transplantation;
autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis,

myasthenia gravis, type I diabetes, and the like;
and infections caused by pathogenic microorganisms (e.g. Aspergillus fumigatus, Fusarium oxysporum, Trichophyton asteroides, and the like).

Furthermore, pharmaceutical preparations of the histone deacetylase inhibitor, such as the compound [I], are useful for the therapy or prophylaxis of the following diseases.

Inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated diseases (e.g. psoriasis, atopic dermatitis, contact dermatitis, eczematoid dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, erythema, dermal eosinophilia, lupus erythematosus, acne, and alopecia areata);
autoimmune diseases of the eye (e.g. keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, and the like);
reversible obstructive airways diseases [asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, and dust asthma), particularly chronic or inveterate asthma (e.g. late asthma and airway hyper-responsiveness) bronchitis, and the like];
mucosal or vascular inflammations (e.g. gastric ulcer, ischemic or thrombotic vascular injury, ischemic bowel diseases, enteritis, necrotizing enterocolitis, intestinal damages associated with thermal burns, leukotriene B4-mediated diseases);
intestinal inflammations/allergies (e.g. coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis);
food-related allergic diseases with symptomatic manifestation remote from the gastrointestinal tract (e.g. migrain, rhinitis and eczema);
renal diseases (e.g. intestitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome, and diabetic nephropathy);

nervous diseases (e.g. multiple myositis, Guillain-Barre syndrome, Meniere's disease, multiple neuritis, solitary neuritis, cerebral infarction, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and radiculopathy);
cerebral ischemic diseases (e.g., head injury, hemorrhage in brain (e.g., subarachnoid hemorrhage, intracerebral hemorrhage), cerebral thrombosis, cerebral embolism, cardiac arrest, stroke, transient ischemic attack (TIA), and hypertensive encephalopathy);
endocrine diseases (e.g. hyperthyroidism, and Basedow's disease);
hematic diseases (e.g. pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, and anerythroplasia);
bone diseases (e.g. osteoporosis);
respiratory diseases (e.g. sarcoidosis, pulmonary fibrosis, and idiopathic interstitial pneumonia);
skin diseases (e.g. dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photosensitivity, and cutaneous T-cell lymphoma);
circulatory diseases (e.g. arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, and myocardosis);
collagen diseases (e.g. scleroderma, Wegener's granuloma, and Sjögren's syndrome);
adiposis;
eosinophilic fasciitis;
periodontal diseases (e.g. damage to gingiva, periodontium, alveolar bone or substantia ossea dentis);
nephrotic syndrome (e.g. glomerulonephritis);
male pattern alopecia, alopecia senile;
muscular dystrophy;
pyoderma and Sezary syndrome;
chromosome abnormality-associated diseases (e.g. Down's syndrome);
Addison's disease;
active oxygen-mediated diseases [e.g. organ injury (e.g. ischemic circulation disorders of organs (e.g. heart, liver, kidney, digestive tract, and the like) associated with preservation, transplantation, or ischemic diseases (e.g. thrombosis, cardial

infarction, and the like):
intestinal diseases (e.g. endotoxin shock, pseudomembranous colitis, and drug- or radiation-induced colitis):
renal diseases (e.g. ischemic acute renal insufficiency, chronic renal failure):
pulmonary diseases (e.g. toxicosis caused by pulmonary oxygen or drugs (e.g. paracort, bleomycin, and the like), lung cancer, and pulmonary emphysema):
ocular diseases (e.g. cataracta, iron-storage disease (siderosis bulbi), retinitis, pigmentosa, senile plaques, vitreous scarring, corneal alkali burn):
dermatitis (e.g. erythema multiforme, linear immunoglobulin A bullous dermatitis, cement dermatitis):
and other diseases (e.g. gingivitis, periodontitis, sepsis, pancreatitis, and diseases caused by environmental pollution (e.g. air pollution), aging, carcinogen, metastasis of carcinoma, and hypobaropathy)];
diseases caused by histamine release or leukotriene C4 release;
restenosis of coronary artery following angioplasty and prevention of postsurgical adhesions;
autoimmune diseases and inflammatory conditions (e.g., primary mucosal edema, autoimmune atrophic gastritis, premature menopause, male sterility, juvenile diabetes mellitus, pemphigus vulgaris, pemphigoid, sympathetic ophthalmitis, lens-induced uveitis, idiopathic leukopenia, active chronic hepatitis, idiopathic cirrhosis, discoid lupus erythematosus, autoimmune orchitis, arthritis (e.g. arthritis deformans), or polychondritis);
Human Immunodeficiency Virus (HIV) infection, AIDS;
allergic conjunctivitis;
hypertrophic cicatrix and keloid due to trauma, burn, or surgery.

Therefore, the pharmaceutical composition of the present invention is useful for the therapy and prophylaxis of liver diseases [e.g. immunogenic diseases (e.g. chronic autoimmune liver diseases such as autoimmune hepatic diseases, primary biliary cirrhosis or sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxins, viral hepatitis, shock, or anoxia), hepatitis B, non-A non-B hepatitis, hepatocirrhosis, and hepatic failure (e.g. fulminant hepatitis, late-onset hepatitis and "acute-on-chronic" liver

failure (acute liver failure on chronic liver diseases))].

The pharmaceutical composition of the present invention can be used in the form of pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the histone deacetylase inhibitor, such as the compound [I], as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral administrations. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, injections, ointments, liniments, eye drops, lotion, gel, cream, and any other form suitable for use.

The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in a solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening, solubilizing and coloring agents and perfumes may be used.

For applying the composition to human, it is preferable to apply it by intravenous, intramuscular, topical or oral administration. While the dosage of therapeutically effective amount of the histone deacetylase inhibitor, such as the compound [I], varies from and also depends upon the age and condition of each individual patient to be treated, when an individual patient is to be treated, in the case of intravenous administration, a daily dose of 0.01-10 mg of the histone deacetylase inhibitor, such as the compound [I], per kg weight of human being, in the case of intramuscular administration, a daily dose of 0.1-10 mg of the histone deacetylase inhibitor, such as the compound of the formula [I], per kg weight of human being, and in the case of oral administration, a daily dose of 0.5-50 mg of the histone deacetylase inhibitor, such as the compound [I], per kg weight of human being, is generally given for treatment.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a stirred solution of 2(S)-(+)-amino-2-methylbutanoic

acid monohydrate (15 g) in 1,4-dioxane (225 ml), a mixture of 1N sodium hydroxide aqueous solution (111 ml) and di-tert-butyl dicarbonate (24.2 g) was added at ambient temperature and the resulting mixture was stirred for 53 hours. Additional mixture of di-tert-butyl dicarbonate (24.2 g) and 1N sodium hydroxide aqueous solution (111 ml) was added at 8 hours, 24 hours and 48 hours after the start of the reaction. The mixture was diluted with diethyl ether (400 ml) and the organic phase was separated. The pH of the aqueous phase was adjusted to 1 with concentrated hydrochloric acid. The aqueous phase was extracted with ethyl acetate (500 ml) twice and the organic layers were combined, washed with brine (500 ml), dried over anhydrous sodium sulfate and concentrated in vacuo. The residual solid was treated with hexane (100 ml) and the resulting suspension was stirred in an ice bath for one hour. The precipitate was filtered and washed with cold hexane to afford 2(S)-N-tert-butoxycarbonylamino-2-methylbutanoic acid (21.71 g, hereinafter Compound a) as a white amorphous solid.

^{1}H-NMR (300MHz, DMSO-d_6, δ): 6.82 (1H, brs), 1.61-1.82 (2H, m), 1.36 (9H, s), 0.75 (3H, t, J=7.5Hz);
MASS (ES-): m/e 216.17.

Preparation 2

To a solution of (S)-2-amino-6-hydroxyhexanoic acid (2.0 g) and sodium hydrogen carbonate (2.28 g) in dioxane-water mixture (20 ml : 20 ml) was added di-tert-butyl dicarbonate (5.93 g) at room temperature. The resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was diluted with water and washed with ether. The aqueous phase was adjusted to pH 2 with conc. hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give 2(S)-N-tert-butoxycarbonylamino-6-hydroxyhexanoic acid as a solid.

^{1}H-NMR (300MHz, DMSO-d_6, δ): 1.18-1.45 (4H, m), 1.37 (9H, s), 1.45-1.70 (2H, m), 3.35 (2H, m), 3.75-3.88 (1H, m), 4.31-4.45 (1H, br), 7.06 (1H, d, J=7.5Hz);
MASS (ES-): m/e 246.15 (M-1).

Preparation 3

To a solution of 2(S)-N-tert butoxycarbonylamino-6-hydroxyhexanoic acid (3.36 g) in N,N-dimethylformamide (35 ml),

cesium carbonate powder was added (2.21 g) at 0°C and stirred for 1.5 hours at room temperature. To the mixture, benzylbromide (1.66 ml) was added at 0°C and stirred for 1.5 hours. The reaction mixture was stirred for further 1.5 hours at room temperature. The reaction mixture was poured into water under ice-cooling and extracted with ethyl acetate. The organic layer was washed with water (3 times) and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give 2(S)-N-tert-butoxycarbonylamino-6-hydroxyhexanoic acid benzyl ester as a pale yellow crude oil.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.44 (9H, s), 1.48-1.90 (7H, m), 3.55-3.65 (2H, m), 4.30-4.41 (1H, m), 5.02-5.10 (1H, m), 5.10-5.25 (2H, m), 7.36 (5H, br.s);

MASS (ES-): m/e 338.23 (M+1).

Preparation 4

To a solution of 2(S)-N-tert-butoxycarbonylamino-6-hydroxyhexanoic acid benzyl ester (4.58 g) in pyridine (13 ml), benzoylchloride (2 g) was added at 0°C and stirred for 1.5 hours at room temperature. The reaction mixture was poured into cooled 1N hydrochloric acid (150 ml) and stirred for 10 minutes. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated sodium hydrogen carbonate, water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography (eluting with ethyl acetate/hexane = 10/1 to 4/1 v/v) to give 2(S)-N-tert-butoxycarbonylamino-6-benzoyloxyhexanoic acid benzyl ester as a pale yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.35-1.60 (2H, m), 1.43 (9H, s), 1.62-1.96 (4H, m), 4.26 (1H, t, J=6.0Hz), 4.30-4.42 (1H, m), 5.00-5.08 (1H, m), 5.08-5.22 (2H, m), 7.34 (5H, s), 7.39-7.46 (2H, m), 7.52-7.60 (1H, m), 7.98-8.05 (2H, m);

MASS (ES+): m/e 442.34.

Preparation 5

To a solution of 2(S)-N-tert-butoxycarbonylamino-6-benzoyloxyhexanoic acid benzyl ester (5.43 g) in methanol (55 ml), palladium hydroxide on charcoal catalyst (50 mg) was added. The air atmosphere was replaced with hydrogen (4 atm) and shaken for 3 hours. The resulting mixture was filtered through a pad of Celite®, and washed with methanol. The filtrate was concentrated

in vacuo to give 6-benzoyloxy-2(S)-N-tert-butoxycarbonylamino-hexanoic acid (hereinafter Compound b) as a pale yellow oil.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.44 (9H, s), 1.47-2.05 (6H, m), 4.12-4.27 (1H, m), 4.44 (2H, t, J=6.0Hz), 5.00-5.12 (1H, m), 7.38-7.50 (2H, m), 7.50-7.62 (1H, m), 8.00-8.07 (2H, m);
MASS (ES+): m/e 352.20 (M+1).

Preparation 6

To a cooled suspension of N-tert-butoxycarbonylamino-6-methoxy-6-oxo-L-norleucine dicyclohexylamine salt (21.1 g) in N,N-dimethylformamide (210 ml) was added benzyl bromide (7.9 g), and the mixture was stirred at ambient temperature for 3 days. The mixture was evaporated in vacuo. The residue was diluted with ethyl acetate and the remaining solid was filtered off. The filtrate was washed with 10% aqueous citric acid solution, saturated sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (eluting with hexane/ethyl acetate = 4:1 to 2:1 v/v) to give N-tert-butoxycarbonyl-6-methoxy-6-oxo-L-norleucine benzyl ester (15.4 g) as a white solid.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.28 (3x3H, s), 1.59-1.75 (3H, m), 1.83 (1H, m), 2.31 (2H, m), 3.65 (3H, s), 4.35 (1H, m), 5.06 (1H, br-d, J=8Hz), 5.14 (1H, d, J=12Hz), 5.20 (1H, d, J=12Hz), 7.30-7.42 (5H, m);
MASS (ES+): m/e 366.

Preparation 7

To a stirred solution of N-tert-butoxycarbonyl-6-methoxy-6-oxo-L-norleucine benzyl ester (15.4 g) in acetonitrile (150ml) were added 4-dimethylaminopyridine (1.03 g) and di-tert-butyldicarbonate (14.7 g), and the mixture was stirred at ambient temperature for 1 day. The mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography (eluting with hexane/ethyl acetate = 10:1 v/v) to give N,N-di-tert-butoxycarbonyl-6-methoxy-6-oxo-L-norleucine as a colorless oil (20.0 g).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.45 (2x9H, s), 1.70 (2H, m), 1.96 (1H, m), 2.15 (1H, m), 2.36 (2H, m), 3.66 (3H, s), 4.90 (1H, dd, J=9 and 4.5Hz), 5.13 (1H, d, J=11Hz), 5.17 (1H, d, J=11Hz), 7.28-7.39 (5H, m);

MASS (ES+): m/e 488.

Preparation 8

To a cooled solution of N,N-di-tert-butoxycarbonyl-6-methoxy-6-oxo-L-norleucine (9.71 g) in diethyl ether (150 ml) was added dropwise 1M solution of diisobutylaluminium hydride in hexane (DIBAL) (23 ml) at -78°C. After 30 minutes DIBAL (24 ml) was added dropwise until the starting compound was disappeared. The reaction mixture was quenched by addition of water. After warming to 0°C with stirring, the mixture was filtered through a pad of Celite®. The solvent was evaporated and the residual solvent was removed azeotropically with toluene to give N,N-di-tert-butoxycarbonyl-6-oxo-L-norleucine benzyl ester as a pale yellow oil (8.94 g).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.45 (2x9H, s), 1.70 (2H, m), 1.96 (1H, m), 2.14 (1H, m), 2.49 (2H, m), 4.90 (1H, m), 5.13 (1H, d, J=12Hz), 5.17 (1H, d, J=12Hz), 7.26-7.39 (5H, m), 9.76 (1H, t, J=1Hz);

MASS (ES-): m/e 435.

Preparation 9

To a stirred solution of dimethyl (3R)-3-benzyloxy-2-oxobutylphosphonate (1.08 g), lithium chloride (174 mg), and N,N-diisopropylethylamine (442 mg) in acetonitrile (10 ml) was added a solution of N,N-di-tert-butoxycarbonyl-6-oxo-L-norleucine benzyl ester (1.49 g) in acetonitrile (30 ml) at ambient temperature. The mixture was stirred at ambient temperature for 5 days. After evaporation of the solvent, the residue was diluted with water, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (eluting with hexane/ethyl acetate = 10:1 v/v) to give benzyl (2S,6E)-9-benzyloxy-2-di-tert-butoxycarbonylamino-8-oxodec-6-enoate as an oil (1.13 g).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.35 (3H, d, J=7Hz), 1.38-1.62 (6H, m), 1.44 (2x9H, s), 1.95 (1H, m), 2.16 (1H, m), 2.28 (2H, m), 4.05 (1H, q, J=7Hz), 4.41 (1H, d, J=12Hz), 4.56 (1H, d, J=12Hz), 4.90 (1H, dd, J=10 and 5Hz), 5.12 (1H, d, J=12Hz), 5.16 (1H, d, J=12Hz), 6.51 (1H, d, J=15Hz), 7.02 (1H, dt, J=15 and 7Hz), 7.23-7.40 (5H, m);

MASS (ES+): m/e 618 (M+Na).

Preparation 10

A solution of benzyl (2S,6E)-9-benzyloxy-2-di-tert-butoxycarbonylamino-8-oxodec-6-enoate (2.74 g) in ethyl acetate (30 ml) was hydrogenated in the presence of 10% palladium-carbon (300 mg) for 2 hours. The reaction mixture was filtered through a pad of Celite® and concentrated in vacuo to give (2S)-9-benzyloxy-2-di-tert-butoxycarbonylamino-8-oxodecanoic acid as an oil (2.27 g).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.19-1.53 (6H, m), 1.33 (3H, d, J=7Hz), 1.50 (2x9H, s), 1.89 (1H, m), 2.07 (1H, m), 2.44-2.65 (2H, m), 3.92 (1H, q, J=7Hz), 4.48 (1H, d, J=12Hz), 4.54 (1H, d, J=12Hz), 4.89 (1H, dd, J=10 and 5Hz), 7.22-7.40 (5H, m);
MASS (ES-): m/e 506.

Preparation 11

To a solution of (2S)-9-benzyloxy-2-di-tert-butoxycarbonylamino-8-oxodecanoic acid (164 mg) in dioxane (2 ml) was added 4N-hydrogen chloride in dioxane (2 ml), and the mixture was stirred at ambient temperature for 3 hours. The solvent was evaporated in vacuo and the residual solvent was removed azeotropically with toluene to give (2S)-2-amino-9-benzyloxy-8-oxodecanoic acid hydrochloride as an amorphous (109 mg).

^{1}H-NMR (300MHz, DMSO-d_6, δ): 1.16-1.53 (6H, m), 1.23 (3H, d, J=7Hz), 1.76 (2H, m), 2.55 (2H, m), 3.86 (1H, t, J=5Hz), 3.99 (1H, q, J=7Hz), 4.46 (1H, d, J=12Hz), 4.51 (1H, d, J=12Hz), 7.26-7.41 (5H, m), 8.30 (2H, br);
MASS (ES+): m/e 308.

Preparation 12

To a stirred solution of (2S)-2-amino-9-benzyloxy-8-oxodecanoic acid hydrochloride (1.37 g) in dioxane (20 ml) were added 1N-sodium hydroxide (8.8 ml) and di-tert-butyldicarbonate (1.04 g) in dioxane, and the mixture was stirred at ambient temperature for 4 hours. The mixture was concentrated in vacuo. The residue was diluted with water and the mixture was washed with diethyl ether. The aqueous phase was acidified with 1N-hydrogen chloride, and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give (2S)-9-benzyloxy-2-tert-butoxycarbonylamino-8-oxodecanoic acid (hereinafter Compound c) as a colorless oil (1.48 g).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.21-1.46 (4H, m), 1.33 (3H, d, J=7Hz), 1.52-1.74 (3H, m), 1.84 (1H, m), 2.55 (2H, m), 3.72 (1H, q, J=7Hz), 4.28 (1H, m), 4.49 (1H, d, J=12Hz), 4.55 (1H, d, J=12Hz), 4.97 (1H, br-d, J=8Hz), 7.21-7.40 (5H, m);
MASS (ES-): m/e 406.

Preparation A

Preparation A1

Preparation A1-1

To a stirred solution of N-tert-butoxycarbonyl-(R)-proline (50 g) in N,N-dimethylformamide (250 ml), cesium carbonate (37.8 g) was added portionwise under ice-cooling in an ice bath. The ice bath was removed and the suspension was stirred at ambient temperature for 1.5 hours. To the suspension benzyl bromide (40.9 g) was added under ice-cooling and the mixture was stirred at ambient temperature for two and half an hour. To this mixture, water (250 ml) was added under ice-cooling and the mixture was extracted with ethyl acetate (1500 ml), and washed with water (250 ml, 3 times) and brine (250 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo to give crude Compound A1-1 (N-tert-butoxycarbonyl-(R)-proline benzyl ester, 87.3 g) as a colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.35 (6H, s), 1.46 (3H, s), 1.76-2.04 (3H, m), 2.07-2.31 (1H, m), 3.31-3.61 (2H, m), 4.26 (0.6H, dd, J=8.0 and 3.6Hz), 4.40 (0.4H, dd, J=8.4 and 2.4Hz), 5.04-5.30 (2H, m), 7.25-7.40 (5H, m);
MASS (ES+): m/e 306.13 (M+1).

Preparation A1-2

To the Compound A1-1 (114 mg), 4N hydrogen chloride in ethyl acetate (50 ml) was added at ambient temperature and the mixture was stirred at ambient temperature for 2 hours. The mixture was concentrated in vacuo and the residual hydrogen chloride was removed azeotropically with ethyl acetate 4 times.

The residual amorphous solid was dissolved in N,N-dimethylformamide (3 ml), and to the solution were added O-benzyl-N-tert-butoxycarbonyltyrosine (146 mg), 1-ethyl-3-(3'-N,N-dimethylaminopropyl)carbodiimide (63.8 mg) and 1-hydroxybenzotriazole (55.5 mg) under ice-cooling. The mixture was stirred at ambient temperature for 1.5 hours. The mixture was

diluted with ethyl acetate (300 ml) and washed with 5% aqueous potassium hydrogensulfate solution (200 ml, 4 times), saturated aqueous sodium bicarbonate solution (300 ml, twice) and brine (300 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography eluted with ethyl acetate-hexane (1:1 v/v) to give Compound A1-2 (201 mg) as a colorless amorphous solid.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 7.45-7.25 (10H, m), 7.11 (2H, d, J=8Hz), 6.87 (2H, d, J=8Hz), 5.37 (1H, br.d, J=8.4Hz), 5.24-4.95 (2H, m), 4.64-4.52 (1H, m), 4.31 (1H, dd, J=7.3 and 4.8Hz), 3.55-3.45 (2H, m), 3.00 (1H, dd, J=12.8 and 5.6Hz), 2.86 (1H, dd, J=12.8 and 9.6Hz), 2.70-2.55 (1H, m), 1.92-1.70 (2H, m), 1.60 (1H, m), 1.43 (9H, s);

MASS (ES+): m/e 559.36 (M+1).

Preparation A1-3

To the Compound A1-2 (6.21 g) was added 4N hydrogen chloride in ethyl acetate (100 ml) under ice-cooling and the mixture was stirred at ambient temperature for one hour. The mixture was concentrated in vacuo and the residual hydrogen chloride was removed 4 times azeotropically with ethyl acetate.

The residual amorphous solid was dissolved in N,N-dimethylformamide (60 ml), then Compound a (2.42 g), PyBOP® (6.36 g) (Nova biochem, benzotriazol-1-yloxy-tris-pyrrolidino-phosphonium hexafluorophosphate) and N,N-diisopropylethylamine (4.74 g) were added to this solution, and the resulting mixture was stirred at ambient temperature for 16 hours. The volatiles were removed in vacuo and the residue was extracted with ethyl acetate (500 ml).

The organic phase was washed with aqueous 5% potassium hydrogensulfate solution (100 ml, 4 times), saturated aqueous sodium bicarbonate solution (100 ml, 4 times), water (100 ml) and brine (100 ml). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluting with ethyl acetate/hexane = 2:1 v/v) to give Compound A1-3 (5.10 g) as an amorphous solid.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 7.55-7.20 (10H, m), 7.10 (2H, d, J=7.6Hz), 7.00-6.73 (3H, m), 5.20-4.96 (3H, m), 4.94-4.80 (1H, m),

4.49-4.30 (1H, m), 3.61-3.44 (2H, m), 3.00 (1H, dd, J=13.0 and 5.4Hz), 2.86 (1H, dd, J=13.0 and 8.8Hz), 2.75-2.60 (1H, m), 2.06-1.35 (5H, m), 1.43 (9H, s), 0.80 (3H, t, J=6.3Hz);
MASS (ES+): m/e 658.43 (M+1).

Preparation A1-4

To the Compound A1-3 (5.59 g) was added 4N hydrogen chloride in ethyl acetate (50 ml) under ice-cooling and the mixture was stirred at ambient temperature for 1 hour. The mixture was concentrated in vacuo and the residual hydrogen chloride was removed 4 times azeotropically with ethyl acetate.

The residue was dissolved in dichloromethane (50 ml) and to this solution was added Compound b (3.14 g), PyBOP® (4.86 g) and N,N-diisopropylethylamine (3.62 g) under ice-cooling, and the resulting mixture was stirred at ambient temperature for 16 hours. The volatiles were removed in vacuo and the residue was extracted with ethyl acetate (500 ml). The organic phase was washed with 5% aqueous potassium hydrogensulfate solution (200 ml, 4 times), saturated aqueous sodium bicarbonate solution (200 ml, twice), water (200ml, twice) and brine (100 ml). The residue was purified by flash chromatography (eluting with ethyl acetate/hexane = 2:1 v/v) to give Compound A1-4 (5.2 g) as a colorless amorphous solid.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 8.10-7.98 (2H, m), 7.60-7.22 (13H, m), 7.14-6.77 (5H, m), 6.69 (1H, br.d, J=6.7Hz), 5.18-4.95 (5H, m), 4.93-4.83 (1H, m), 4.39-4.32 (1H, m), 4.31 (2H, t, J=6.6Hz), 4.12-4.02 (1H, m), 3.61-3.49 (2H, m), 3.03-2.85 (2H, m), 2.82-2.70 (1H, m), 2.36-2.19 (1H, m), 1.98-1.38 (10H, m), 1.50 (3H, s), 1.44 (9H, s), 0.72 (3H, t, J=7.3Hz);
MASS (ES+): m/e 891.49 (M).

Preparation A1-5

A solution of the Compound A1-4 (5.43 g) in ethyl acetate (110 ml) was hydrogenated in the presence of palladium hydroxide and 20 wt% Pd (dry basis) on carbon (Pearlman's catalyst) (540 mg) for 4 hours under atmosphere pressure. The catalyst was filtered off through a pad of Celite® and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with chloroform/methanol = 10:1 v/v to give Compound A1-5 as a colorless amorphous (4.96 g).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.78 (3H, t, J=7.0Hz), 1.44 (9H, s), 1.30-2.00 (13H, m), 2.06-2.19 (1H, m), 2.64-2.77 (1H, m), 2.95

(2H, br.d, J=6.6Hz), 3.55-3.69 (1H, m), 3.94-4.07 (1H, m), 4.25-4.38 (3H, m), 4.87 (1H, m), 5.05 (2H, s), 6.82 (1H, s), 6.87 (2H, d, J=8.5Hz), 7.11 (2H, d, J=8.5Hz), 7.20 (1H, br.d, J=8.8Hz), 7.27-7.60 (8H, m), 7.99-8.07 (2H, m);
MASS (ES+): m/e 801.47 (M+1).

Preparation A1-6

To the Compound A1-5 (4.96 g) was added 4N hydrogen chloride in ethyl acetate (60 ml) under ice-cooling and the mixture was stirred at ambient temperature for 3 hours. The solvent was concentrated in vacuo and the residual hydrogen chloride was removed azeotropically with ethyl acetate (100 ml, 4 times). The residue was dried in vacuo to give Compound A1-6 (4.64 g) as a pale brown amorphous solid. The obtained compound was used in the Preparation C1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.60-0.82 (3H, m), 1.25-2.20 (15H, m), 2.74-3.07 (4H, m), 3.63-3.79 (1H, m), 4.13-4.38 (3H, m), 4.82-4.95 (1H, m), 4.99 (2H, s), 6.83 (2H, d, J=7.3Hz), 7.10 (2H, d, J=7.3Hz), 7.20-7.54 (8H, m), 7.51 (1H, t, J=8.1Hz), 7.57-7.70 (1H, m), 7.99 (2H, d, J=7.0Hz), 8.07-8.40 (2H, m);
MASS (ES+): m/e 701.36 (free+1).

Preparation A2

Preparation A2-2

The Compound A1-1 (10.0 g) was dissolved in ethyl acetate (60 ml) and the mixture was stirred for 4 hours at ambient temperature. The solvent was evaporated and the residual solvent was removed azeotropically with toluene. The residue was washed with ethyl acetate and dried to give D-proline benzyl ester hydrochloride (hereinafter Compound d).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.92 (2H, m), 2.01 (1H, m), 2.28 (1H, m), 3.22 (1H, m), 4.44 (1H, dd, J=8 and 7Hz), 5.23 (1H, d, J=12Hz), 5.26 (1H, d, J=12Hz), 7.23-7.47 (5H, m);
MASS (ES+): m/e 206.

N-t-Butoxycarbonyl O-methyl-L-tyrosine (3.62 g) was dissolved in dichloromethane (40 ml), then Compound d (2.82 g), hydroxybenzotriazol (1.73 g) and a solution of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrogen chloride (1.99 g) in dichloromethane (5 ml) were added to the mixture and the mixture was stirred for 14 hours at ambient temperature. The reaction mixture was added to 10% aqueous solution of citric acid (50 ml)

then 5% aqueous solution of potassium hydrogensulfate (50 ml) was added to the mixture. The mixture was washed with saturated aqueous sodium bicarbonate (50 ml) and saturated aqueous sodium chloride (50 ml) then dried over magnesium sulfate, and evaporated to dryness to give a crude compound. The crude compound was purified by flash column chromatography (Silica gel 60, Spherical, 120 g, eluent: ethyl acetate : hexane = 1:2 to 1:1) to give Compound A2-2 (5.55 g).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.43 (3x3H, s), 1.55 (1H, m), 1.74-2.00 (3H, m), 2.69 (1H, m), 2.87 (1H, dd, J=13.9Hz), 3.00 (1H, dd, J=13 and 5Hz), 3.54 (1H, m), 4.36 (1H ,dd, J=8 and 4Hz), 4.60 (1H, m), 5.11 (1H, d, J=12.5Hz), 5.19 (1H, d, J=12.5Hz), 5.37 (1H, d, J=9Hz), 6.79 (2X1H, d, J=8.5Hz), 7.12 (2X1H, d, J=8.5Hz), 7.28-7.40 (5H, m);

MASS (ES+): m/e 483.

Preparation A2-3

The Compound A2-2 (5.50 g) was dissolved in ethyl acetate (30 ml) and a cold solution of 4N hydrogen chloride in ethyl acetate (50 ml) was added to the mixture and stirred for 2.5 hours at ambient temperature. The mixture was evaporated to dryness to give Compound e (4.97 g) as a white foam.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.60 (1H, m), 1.70-1.87 (2H, m), 1.97 (1H, m), 2.80 (1H, m), 2.91 (1H, dd, J=13 and 8Hz), 3.06 (1H, dd, J=13 and 6Hz), 3.58 (1H, m), 4.30 (1H, dd, J=9 and 3Hz), 4.36 (1H, m), 5.08 (1H, d, J=13Hz), 5.19 (1H, d, J=13Hz), 6.90 (2 X 1H, d, J=8Hz), 7.14 (2 X 1H, d, J=8Hz), 7.30-7.44 (5H, m), 8.34 (2H, br);

MS (ES+): m/e 383.

The Compound e (4.89 g) was dissolved in dichloromethane (40 ml) and Compound a (4.31g), benzotriazol-1-yloxy-tris-pyrrolidinophosphonium hexafluorophosphate (6.68 g) and N-ethyldiisopropylamine (4.83 g) were added to the solution, and the mixture was stirred for 15 hours at ambient temperature. The mixture was diluted with chloroform (40 ml), washed with 5% aqueous solution of potassium hydrogensulfate (50 ml), saturated sodium bicarbonate (50 ml) and saturated sodium chloride (50 ml), dried over sodium sulfate and evaporated to give a crude compound. The crude compound was purified by flash column chromatography (Silica gel 60N, Spherical, 120 g, eluent: ethyl acetate : hexane

= 1:2 to 1:1) to give Compound A2-3 (5.70 g).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.81 (3H, t, J=7.5Hz), 1,41 (3H, s), 1,44 (9H, s), 1.58 (1H, m), 1.76-2.06 (5H, m), 2.75 (1H, m), 2.89 (1H, dd, J=13 and 9Hz), 3.02 (1H, dd, J=13 and 5Hz), 3.56 (1H, m), 3.77 (3H, s), 4.38 (1H, dd, J=8 and 4Hz), 4.91 (1H, ddd, J=9, 8.5 and 5Hz), 5.11 (1H, d, J=12.5Hz), 5.15 (1H, d, J=12.5Hz), 6.80 (2H, d, J=8.5Hz), 6.84 (1H, d, J=8.5Hz), 7.13 (2H, d, J=8.5Hz), 7.28-7.40 (5H, m);
MASS (ES+): m/e 582.

Preparation A2-4

The Compound A2-3 (5.31 g) was dissolved in ethyl acetate (30 ml) and cold solution of 4N hydrogen chloride in ethyl acetate (50 ml) was added to the mixture and stirred for 1 hour at ambient temperature. The mixture was evaporated to dryness to give Compound f (5.31 g) as a white foam.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.75 (3H, d, J=7Hz), 1.33 (3H, s), 1.63-2.30 (6H, m), 2.84 (1H, dd, J=13 and 10Hz), 2.93 (1H, dd, J=13 and 5Hz), 3.51 (1H, m), 3.74 (1H, m), 4.34 (1H, dd, J=9 and 4Hz), 4.80 (1H, ddd, J=9Hz), 7.20 (2 X 1H, d, J=9Hz), 7.29-7.45 (1H, m), 8.03 (2H, br-s), 8.64 (1H, d, J=9Hz);
MS (ES+): m/e 482.

The Compound f (5.26 g) was dissolved in dichloromethane (30 ml) and a solution of Compound b (3.57g) in dichloromethane (50 ml), benzotriazol-1-yloxy-tris-pyrrolidinophosphonium hexafluorophosphate (6.34 g) and N-ethyldiisopropylamine (4.2 g) were added to the solution, and the mixture was stirred for 12 hours at ambient temperature. The mixture was diluted with chloroform (80 ml), washed with 5% aqueous solution of potassium hydrogensulfate (100 ml), saturated sodium bicarbonate (100 ml) and saturated sodium chloride (100 ml), dried over sodium sulfate and evaporated to give a crude compound. The crude compound was purified by flash column chromatography (Silica gel 60N, Spherical, 150 g, eluent: ethyl acetate : hexane = 1:1 to 1:2) to give Compound A2-4 (5.76 g).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.72 (3H, t, J=7.3Hz), 1.43 (3H, s), 1.44 (3X3H, s), 1.47-2.36 (12H, m), 2.84 (1H, m), 2.92 (1H, dd, J=13 and 9.5Hz), 2.98 (1H, dd, J=13 and 5.5Hz), 3.58 (1H, m), 3.77 (3H, s), 4.08 (1H, m), 4.32 (2H, t, J=6.5Hz), 4.39 (1H, dd, J=8 and 4Hz), 4.91 (1H, m), 5.12 (1H, m), 5.13 (2H, s), 6.70 (1H,

br-d, J=9Hz), 6.80 (2X1H, d, J=8.5Hz), 7.01 (1H, s), 7.10 (2X1H, d, J=8.5Hz), 7.28-7.36 (5H, m), 7.43 (2X1H, dd, J=7.5 and 7.5Hz), 7.55 (1H, dd, J=7.5 and 7.5Hz), 8.03 (2X1H, d, J=7.5Hz);
MASS (ES-): m/e 813.

Preparation A2-5

Compound A2-5 was obtained in a manner similar to Preparation A1-5 except that Compound A2-4 was used instead of the Compound A1-4 and palladium on carbon was used instead of the Pearlman's catalyst.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.77 (3H, t, J=7.5Hz), 1.38-2.36 (12H, m), 1.44 (9+3H, s), 2.79 (1H, m), 2.90-3.02 (2H, m), 3.67 (1H, m), 3.77 (3H, s), 4.02 (1H, m), 4.26-4.42 (3H, m), 4.88 (1H, m), 5.20 (1H, m), 6.81 (2X1H, d, J=8.5Hz), 6.83 (1H, br-s), 7.12 (2X1H, d, J=8.5Hz), 7.24 (1H, d, J=8Hz), 7.43 (2X1H, dd, J=7.5 and 7.5Hz), 7.56 (1H, dd, J=7.5 and 7.5Hz), 8.04 (2X1H, d, J=7.5Hz);
MASS (ES-): m/e 723.

Preparation A2-6

Compound A2-6 was obtained in a manner similar to Preparation A1-6 except that trifluoroacetic acid was used instead of 4N hydrogen chloride. The obtained compound was used in Preparation C2.

^{1}H-NMR (300MHz, DMSO-d_6, δ): 0.54 (3X1/3H, t, J=7.3Hz, 0.66 (3X2/3H, t, J=7.3Hz), 1.31 (3X1/3H, s), 1.35 (3X2/3H, s), 1.44 (2H, m), 1.60-2.20 (10H, m), 2.70-2.98 (2H, m), 3.18 (1H, m), 3.36 (1H, m), 3.67 (3X1/3H, s), 3.69 (3X2/3H, s), 4.12 (1X2/3H, dd, J=9.3Hz), 4.26 (2H, t, J=6Hz), 4.41 (1H, m), 4.77 (1H, m), 4.84 (1X1/3H, dd, J=9.3Hz), 6.78 (2X1/3H, d, J=9Hz), 6.81 (2X2/3H, d, J=9Hz), 7.10-7.30 (3H, m), 7.48-7.60 (2H, m), 7.68 (1H, m), 7.88-8.17 (5H, m);
MASS (ES+): m/e 625.

Preparation A3

Preparation A3-2

Compound A3-2 was obtained in a manner similar to Preparation A1-2 except that Compound g was used instead of o-benzyl-N-tert-butoxycarbonyltyrosine.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.42 (9H, s), 1.50-1.68 (1H, m), 1.80-2.03 (3H, m), 2.71-2.84 (1H, m), 2.92 (1H, dd, J=13.2 and 8.7Hz), 3.00 (1H, dd, J=13.2 and 6.1Hz), 3.53-3.65 (1H, m), 4.36 (1H, dd, J=7.7 and 3.6Hz), 4.62 (1H, dt, J=8.5 and 5.9Hz), 5.10 (1H, d,

J=12.5Hz), 5.20 (1H, d, J=12.5Hz), 5.34 (1H, d, J=8.0Hz), 6.88-7.03 (2H, m), 7.17 (2H, dd, J=8.5 and 5.5Hz), 7.30-7.40 (5H, m); MASS (ES+): m/e 471.37 (M+1).

Preparation A3-3

Compound A3-3 was obtained in a manner similar to Preparation A1-3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.80 (3H, t, J=7.6Hz), 1.39 (3H, s), 1.43 (9H, s), 1.76-2.03 (6H, m), 2.74-2.87 (1H, m), 2.95 (1H, dd, J=13.2 and 9.1Hz), 3.03 (1H, dd, J=13.2 and 4.8Hz), 3.51-3.66 (1H, m), 4.38 (1H, dd, J=8.1 and 3.7Hz), 4.87-4.98 (1H, m), 4.98-5.20 (3H, m), 6.81-7.02 (3H, m), 7.15-7.23 (2H, m), 7.28-7.41 (5H, m); MASS (ES+): m/e 570.42 (M+1).

Preparation A3-4

Compound A3-4 was obtained in a manner similar to Preparation A1-4.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.61 (0.6H, t, J=7.3Hz), 0.72 (2.4H, t, J=7.3Hz), 1.39-2.08 (11H, m), 1.43 (9H, s), 1.48 (3H, s), 2.13-2.33 (1H, m), 2.83-2.99 (1H, m), 2.98 (2H, d, J=7.0Hz), 3.51-3.70 (1H, m), 3.92-4.15 (1H, m), 4.31 (2H, t, J=5.9Hz), 4.39 (1H, dd, J=7.3 and 3.2Hz), 4.92 (1H, q, J=7.3Hz), 5.02-5.15 (2H, m), 5.17 (1H, s), 6.72 (1H, br. s), 6.83-7.05 (3H, m), 7.16 (2H, dd, J=8.4 and 5.5Hz), 7.27-7.38 (5H, m), 7.39-7.47 (2H, m), 7.51-7.60 (1H, m), 8.03 (2H, d, J=7.3Hz); MASS (ES+): m/e 803.55 (M+1).

Preparation A3-5

Compound A3-5 was obtained in a manner similar to Preparation A1-5.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.77 (3H, t, J=7.4Hz), 1.17-2.02 (11H, m), 1.45 (12H, s), 2.11-2.25 (1H, m), 2.79-3.10 (3H, m), 3.64-3.79 (1H, m), 4.26-4.42 (3H, m), 4.92 (1H, q, J=7.6Hz), 5.23 (1H, br.s), 6.79 (1H, br.s), 6.97 (2H, t, J=8.5Hz), 7.19 (2H ,dd, J=8.5 and 5.2Hz), 7.30 (1H, d, J=8.3Hz), 7.39-7.48 (2H, m), 7.52-7.62 (1H, m), 8.04 (2H, d, J=8.5Hz); MASS (ES+): m/e 713.54 (M+1).

Preparation A3-6

Compound A3-6 was obtained in a manner similar to Preparation A1-6. The obtained compound was used in Preparation C3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.70 (3H, t, J=7.4Hz), 1.38 (3H, s),

1.51-2.16 (12H, m), 2.83-3.15 (3H, m), 3.68-3.83 (1H, m), 4.18-4.37 (4H, m), 4.86-4.98 (1H, m), 6.92 (2H, t, J=8.5Hz), 7.17 (2H, dd, J=8.5 and 5.8Hz), 7.39 (2H, t, J=7.7Hz), 7.53 (1H, t, J=7.6Hz), 7.67 (1H, br. s), 7.99 (2H, d, J=7.3Hz), 8.13-8.39 (3H, m);

MASS (ES+): m/e 613.49 (M+1, free).

Preparation A4

Preparation A4-2

Compound A4-2 was obtained in a manner similar to Preparation A1-2.

Preparation A4-3

Compound A4-3 was obtained in a manner similar to Preparation A1-3 except that Compound h was used instead of Compound a.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.31-1.54 (9H, m), 1.55-1.99 (8H, m), 2.01-2.42 (3H, m), 2.52-2.63 (1H, m), 2.80-2.96 (1H, m), 3.03-3.14 (1H, m), 3.44-3.60 (2H, m), 4.31-4,38 (1H, m), 4.68-4.86 (1H, m), 4.94 (1H, dt, J=9.9 and 5.1Hz), 5.05-5.20 (2H, m), 7.08 (1H, d, J=8.1Hz), 7.16-7.39 (10H, m);

MASS (ES+): m/e 564.38 (M+1).

Preparation A4-4

Compound A4-4 was obtained in a manner similar to Preparation A1-4.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.32-2.06 (20H, m), 1.44 (9H, s), 2.09-2.30 (2H, m), 2.64-2.74 (1H, m), 2.88-3.08 (1H, m), 3.53-3.62 (2H, m), 3.98-4.08 (1H, m), 4.27-4.37 (4H, m), 4.85-4.95 (1H, m), 5.07-5.21 (3H, m), 6.63 (1H, s), 7.12-7.37 (6H, m), 7.42 (2H, dd, J=8.1 and 6.9Hz), 7.55 (1H, dd, J=6.9 and 6.9Hz), 8.03 (2H, d, J=8.1Hz);

MASS (ES+): m/e 797.50 (M+1).

Preparation A4-5

Compound A4-5 was obtained in a manner similar to Preparation A1-5.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.16-2.12 (15H, m), 1.44 (9H, s), 2.24-2.41 (1H, m), 2.62-2.76 (1H, m), 2.90-3.09 (2H, m), 3.47-3.50 (1H, m), 3.65-3.77 (1H, m), 4.01-4.11 (2H, m), 4.24-4.38 (4H, m), 4.74-4.84 (1H, m), 5.56-5.64 (1H, m), 6.84-6.92 (1H, m), 7.16-7.31 (6H, m), 7.43 (2H, dd, J=7.8 and 6.9Hz), 7.56 (1H, dd, J=7.8 and 7.8Hz), 8.02 (2H, d, J=6.9Hz);

MASS (ES+): m/e 707.45 (M+1).

Preparation A4-6

Compound A4-6 was obtained in a manner similar to Preparation A1-6. The obtained compound was used in Preparation C4.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.34-2.27 (19H, m), 2.79-3.19 (3H, m), 3.48-3.78 (1H, m), 3.95-4.13 (1H, m), 4.14-4.47 (3H, m), 4.82-5.00 (1H, m), 7.11-7.32 (5H, m), 7.34-7.46 (2H, m), 7.48-7.58 (1H, m), 7.62-7.84 (1H, br. s), 7.95-8.06 (2H, m), 8.06-8.36 (2H, br. s), 8.63-9.02 (1H, br. s);

MASS (ES+): m/e 607.42 (M+1).

Preparation A5

Preparation A5-2

Compound A5-2 was obtained in a manner similar to Preparation A2-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.31 (3H, s), 1.40 (6H, s), 1.56-1.80 (3H, m), 1.84-2.11 (2H, m), 2.92-3.13 (2H, m), 3.57-3.70 (1H, m), 4.36-4.42 (1H, m), 4.62-4.72 (1H, m), 5.04-5.34 (3H, m), 7.11-7.51 (7H, m), 7.54-7.60 (3H, m);

MASS (ES+): m/e 478.40 (M+1).

Preparation A5-3

Compound A5-3 was obtained in a manner similar to Preparation A1-3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.800 (3H, t, J=7.5Hz), 1.36 (3H, s), 1.39 (3H, s), 1.43 (6H, s), 1.52-1.62 (2H, m), 1.67-2.06 (4H, m), 2.83-3.16 (2H, m), 3.50-3.70 (2H, m), 4.36-4.42 (1H, m), 4.86-5.04 (2H, m), 5.06-5.21 (2H, m), 6.87 (1H, d, J=9.0Hz), 7.29-7.48 (6H, m), 7.53-7.59 (3H, m);

MASS (ES+): m/e 577.40 (M+1).

Preparation A5-4

Compound A5-4 was obtained in a manner similar to Preparation A1-4.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.740 (3H, t, J=7.2Hz), 1.30-2.29 (11H, m), 1.34 (3H, s), 1.44 (9H, s), 2.86-3.18 (3H, m), 3.51-3.72 (2H, m), 3.99-4.08 (1H, m), 4.27-4.42 (3H, m), 4.96-5.04 (1H, m), 5.06-5.19 (3H, m), 6.82 (1H, s), 7.12-7.17 (1H, m), 7.28-7.37 (6H, m), 7.39-7.47 (3H, m), 7.52-7.61 (3H, m), 8.00-8.05 (2H, m);

MASS (ES+): m/e 810.59 (M+1).

Preparation A5-5

Compound A5-5 was obtained in a manner similar to Preparation A1-5.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.731 (3H, t, J=7.2Hz), 1.31-2.22 (13H, m), 1.40 (3H, s), 1.44 (9H, s), 2.91-3.23 (3H, m), 3.80-3.94 (1H, m), 3.99-4.13 (1H, m), 4.23-4.43 (3H, m), 4.86-5.00 (1H, m), 5.48-5.60 (1H, m), 6.76 (1H, s), 7.25-7.31 (1H, m), 7.31-7.38 (2H, m), 7.40-7.47 (2H, m), 7.52-7.61 (3H, m), 8.00-8.06 (2H, m);
MASS (ES+): m/e 720.38 (M+1).

Preparation A5-6

Compound A5-6 was obtained in a manner similar to Preparation A1-6. The obtained compound was used in Preparation C5.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.59-0.73 (3H, m), 1.33 (3H, s), 1.52-2.17 (12H, m), 2.92-3.27 (3H, m), 3.70-3.83 (1H, m), 4.14-4.40 (4H, m), 4.90-5.02 (1H, m), 7.31-7.45 (5H, m), 7.49-7.59 (3H, m), 7.59-7.71 (1H, br. s), 7.93-8.11 (5H, m);
MASS (ES+): m/e 620.33 (M+1).

Preparation A6

Preparation A6-2

Compound A6-2 was obtained in a manner similar to Preparation A2-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.39 (3H, t, J=7.2Hz), 1.43 (9H, s), 1.46-1.63 (1H, m), 1.76-2.00 (3H, m), 2.62-2.72 (1H, m), 2.82-2.92 (1H, m), 2.94-3.04 (1H, m), 3.48-3.58 (1H, m), 3.98 (2H, q, J=7.2Hz), 4.32-4.42 (1H, m), 4.53-4.64 (1H, m), 5.10 (1H, d, J=12.6Hz), 5.20 (1H, d, J=12.6Hz), 5.37 (1H, d, J=8.7Hz), 6.78 (2H, d, J=8.7Hz), 7.11 (2H, d, J=8.7Hz), 7.28-7.39 (5H, m);
MASS (ES+): m/e 497.34 (M+1).

Preparation A6-3

Compound A6-3 was obtained in a manner similar to Preparation A1-3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.80 (3H, t, J=7.5Hz), 1.39 (3H, t, J=7.2Hz), 1.40 (3H, s), 1.43 (9H, s), 1.50-1.64 (1H, m), 1.75-2.05 (5H, m), 2.67-2.79 (1H, m), 2.81-2.93 (1H, m), 2.94-3.05 (1H, m), 3.50-3.62 (1H, m), 3.98 (2H, q, J=7.2Hz), 4.37 (1H, dd, J=7.5 and 3.3Hz), 4.90 (1H, dt, J=9.6 and 5.1Hz), 5.10 (1H, d, J=12.3Hz), 5.15 (1H, d, J=12.3Hz), 6.57-6.97 (1H, m), 6.78 (2H, d, J=8.4Hz), 7.11 (2H, d, J=8.4Hz), 7.29-7.39 (5H, m);
MASS (ES+): m/e 596.51 (M+1).

Preparation A6-4

Compound A6-4 was obtained in a manner similar to Preparation A1-4.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.74 (3H, t, J=7.5Hz), 1.40 (3H, t, J=7.2Hz), 1.45 (9H, s), 1.47-1.99 (11H, m), 1.50 (3H, s), 2.18-2.29 (1H, m), 2.76-3.00 (2H, m), 3.44-3.65 (2H, m), 3.99 (2H, q, J=7.2Hz), 4.03-4.13 (1H, m), 4.33 (2H, t, J=6.3Hz), 4.40 (1H, dd, J=7.2 and 3.6Hz), 4.83-4.94 (1H, m), 5.10-5.19 (3H, m), 6.79 (2H, d, J=8.4Hz), 6.92-7.04 (1H, m), 7.10 (2H, d, J=8.4Hz), 7.29-7.39 (6H, m), 7.40-7.48 (2H, m), 7.52-7.60 (1H, m), 8.01-8.07 (2H, m); MASS (ES+): m/e 829.61 (M+1).

Preparation A6-5

Compound A6-5 was obtained in a manner similar to Preparation A1-5.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.79 (3H, t, J=7.5Hz), 1.40 (3H, t, J=7.2Hz), 1.44 (12H, s), 1.57-2.72 (11H, m), 2.65-3.03 (3H, m), 3.58-3.83 (2H, m), 3.99 (2H, q, J=7.2Hz), 4.04-4.15 (1H, m), 4.23-4.39 (3H, m), 4.75-4.88 (1H, m), 5.53-5.63 (1H, m), 6.79 (2H, d, J=8.7Hz), 7.09 (2H, d, J=8.7Hz), 7.13-7.21 (1H, m), 7.39-7.48 (2H, m), 7.52-7.59 (1H, m), 8.00-8.06 (2H, m); MASS (ES+): m/e 739.58 (M+1).

Preparation A6-6

Compound A6-6 was obtained in a manner similar to preparation A1-6. The obtained compound was used in Preparation C6.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.72 (3H, t, J=6.9Hz), 1.34 (3H, s), 1.38 (3H, t, J=7.2Hz), 1.54-2.13 (12H, m), 2.80-3.18 (3H, m), 3.64-3.78 (1H, m), 3.36 (2H, q, J=7.2Hz), 4.14-4.38 (4H, m), 4.77-4.89 (1H, m), 6.77 (2H, d, J=8.7Hz), 7.09 (2H, d, J=8.7Hz), 7.37-7.48 (2H, m), 7.49-7.57 (1H, m), 7.80-8.22 (6H, m); MASS (ES+): m/e 739.58 (free M+1).

Preparation A7

Preparation A7-1

Compound A7-1 was purchased from Kokusan Chemical Co., Ltd.

Preparation A7-2

Fmoc-2-fluorophenylalanine (available from Oakwood Products, Inc.), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (1.29 g) and 1-hydroxybenzotriazole (911 mg) were added to dichloroethane (30 ml), and the mixture was sonicated to

give a homogeneous mixture. To this mixture, Compound A7-1 (1.05 g) in dichloromethane (10 ml) was added and stirred at ambient temperature for 1.3 hours. The reaction mixture was added to 10% aqueous citric acid (30 ml), then the organic layer was collected. To the aqueous layer water (30 ml) was added, then the mixture was extracted with chloroform (50 ml). The organic layer and the chloroform extract were combined, washed with saturated sodium bicarbonate (30 ml) and brine (30 ml), dried over magnesium sulfate, and the solvent was evaporated to give a crude compound. The crude compound was purified by flash column chromatography (Silica gel 60, Spherical, 40g, eluted with ethyl acetate/hexane = 1:2 to 1:1 v/v) to give Compound A7-2 (3.29 g) as a white foam.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.43 (9x4/5H, s), 1.51 (9x1/5H, s), 1.63-2.30 (4H, m), 3.00-3.14 (2H, m), 3.20 (1H, m), 3.70 (1H, m), 4.04-4.42 (4H, m), 4.58 (1x1/5H, m), 4.82 (1x4/5H, m), 5.48 (1x4/5H, d, J=8Hz), 5.71 (1x1/5H, d, J=8Hz), 6.95-7.08 (2H, m), 7.11-7.62 (8H, m), 7.71-7.80 (2H, m);
MASS (ES+): m/e 559.

Preparation A7-3

The Compound A7-2 (3.25 g) was dissolved in acetonitrile (15 ml), N,N-diethylamine (15 ml) was added to the mixture and stirred for 1 hour at ambient temperature. The solvent was evaporated and the residual solvent was removed azeotropically with toluene to give a crude compound. The crude compound was purified by flash column chromatography (Silica gel 60, Spherical, 40-50 μm, eluted with methanol/chloroform = 1:40 v/v) to give Compound i (1.52 g) as a white foam.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.46 (9 X 5/6H, s), 1.47 (9 X 1/6H, s), 1.56-2.25 (4H, m), 2.79 (1 X 1/6H, dd, J=13 and 8Hz), 2.83 (1 X 5/6H, dd, J=13 and 8Hz), 2.94 (1 X 5/6H, dd, J=13 and 7Hz), 3.10 (1 X 1/6H, dd, J=13 and 5Hz), 3.19 (1H, m), 3.62 (1H, m), 3.83 (1H, d, J=8 and 7Hz), 4.28 (1 X 5/6H, dd, J=8 and 4Hz), 4.60 (1 X 1/6H, dd, J=8 and 3Hz), 6.98-7.12 (2H, m), 7.17-7.28 (2H, m);
MASS (ES+): m/e 337.

The Compound i (1.51 g) was dissolved in dichloromethane (20 ml) and Compound j (1.13g), PyBroP® (2.3 g) and N-ethyl-N,N-diisopropylamine (696 mg) were added to the solution, and the mixture was stirred for 5 hours at ambient temperature. The mixture was washed with 10% aqueous solution of citric acid (30

ml), saturated sodium bicarbonate (30 ml) and saturated sodium chloride (30 ml), dried over magnesium sulfate and the solvent was evaporated to give a crude compound. The crude compound was purified by flash column chromatography (Silica gel 60N, Spherical, 40 g, eluent: ethyl acetate : hexane = 1:2 to 1:1) to give Compound A7-3 (1.54 g).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.60 (3x1/4H, t, J=7Hz), 0.75 (3x3/4H, t, J=7.3Hz), 1.33-2.30 (18H, m), 2.98-3.32 (3H, m), 3.50-3.80 (1H, m), 4.25 (1x3/4H, dd, J=8 and 4Hz), 4.67-5.10 (3+1/4H, m), 5.53 (1x1/4H, br), 5.78 (1x3/4H, br), 6.57 (1x1/4H, br), 6.73 (1x3/4H, br-d, J=8Hz), 6.94-7.07 (2H, m), 7.11-7.24 (2H, m), 7.28-7.39 (5H, m);

MASS (ES+): m/e 570.

Preparation A7-4

The Compound A7-3 (1.52 g) was dissolved in methanol and 10% palladium on carbon (150 mg) suspended in water (1 ml) was added to the solution and stirred for 2 hours at ambient temperature, 3 atm. The catalyst was filtered off through a pad of Celite®, the solvent was evaporated, then the residual solvent was removed azeotropically with toluene to give Compound k.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.42 (3 X 1/3H, t, J=7.4Hz), 0.72 (3 X 2/3H, t, J=7.5Hz), 1.19 (3 X 1/3H, s), 1.26 (3 X 2/3H, s), 1.43 (9 X 2/3H, s), 1.51 (9 X 1/3H, s), 1.69-2.30 (6H, m), 2.99-3.30 (3H, m), 3.56-3.77 (1H, m), 4.25 (1 X 2/3H, dd, J=8 and 4Hz), 4.71 (1 X 1/3H, m), 5.02 (1 X 2/3H, m), 5.04 (1 X 1/3H, m), 6.93-7.08 (2H, m), 7.12-7.25 (2H, m);

MASS (ES+): m/e 436.

The Compound k (1.15 g) was dissolved in dichloromethane (15 ml) and a solution of Compound b (1.02 g) in dichloromethane (10 ml), benzotriazole-1-yloxy-tris-pyrrolidinophosphonium hexafluorophosphate (1.65 g) and N-ethyl-N,N-diisopropylamine (751 mg) were added to the solution, and the mixture was stirred for 14 hours at ambient temperature. The mixture was washed with 10% aqueous solution of citric acid (30 ml), saturated sodium bicarbonate (30 ml) and saturated sodium chloride (30 ml), dried over sodium sulfate and the solvent was evaporated to give a crude compound. The crude compound was purified by flash column chromatography (Silica gel 60, Spherical, 50 g, eluent: ethyl acetate : hexane = 1:1 to 2:1) to give Compound A7-4 (1.74 g) as

a white foam.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.60 (3x1/3H, t, J=7.5Hz), 0.71 (3x2/3H, t, J=7.5Hz), 1.34-2.44 (12H, m), 1.41 (9x2/3H, s), 1.43 (9x1/3H, s), 1.49 (3x1/3H, s), 1.51 (3x2/3H, s), 3.00-3.12 (2H, m), 3.23-3.76 (2H, m), 4.07 (1H, m), 4.25 (1H, dd, J=8 and 4Hz), 4.31 (2H, t, J=6.5Hz), 4.67-5.17 (2H, m), 6.54 (1x1/3H, br-d, J=8Hz), 6.70 (1x2/3H, br-d, J=8Hz), 6.93-7.09 (3H, m), 7.10-7.25 (2H, m), 7.43 (2H, dd, J=7.5 and 7.5Hz), 7.56 (1H, dd, J=7.5 and 7.5Hz), 8.03 (2H, d, J=7.5Hz);
MASS (ES-): m/e 767.

Preparation A7-5+6

Compound A7-6 was obtained in a manner similar to Preparation A1-6 except that trifluoroacetic acid was used instead of 4N hydrogen chloride. The obtained compound was used in Preparation C7.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.62 (3H, t, J=7.3Hz), 1.20 (3H, s), 1.49-2.15 (12H, m), 2.88-3.10 (2H, m), 3.34 (1H, m), 3.82 (1H, m), 4.07 (1H, m), 4.23-4.38 (3H, m), 4.92 (1H, m), 6.96-7.11 (2H, m), 7.14-7.28 (3H, m), 7.42 (2H, dd, J=7.6 and 7.6Hz), 7.50-7.58 (2H, m), 7.82 (2H, br), 8.01 (2H, d, J=7.6Hz);
MASS (ES+): m/e 613.

Preparation A8

Preparation A8-6

Compound A8-6 was obtained in a manner similar to Preparation A1-6. The obtained compound was used in Preparation C8.

Preparation A9

Preparation A9-6

Compound A9-6 was obtained in a manner similar to Preparation A1-6. The obtained compound was used in Preparation C9.

Preparation A10

Preparation A10-4

Compound A10-4 was obtained in a manner similar to Preparation A1-4.

Preparation A10-5+6

Compound A10-6 was obtained in a manner similar to Preparation A1-6 except that trifluoroacetic acid was used instead of 4N hydrogen chloride. The obtained compound was used

in Preparation C10.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.70 (3H, t, J=7Hz), 1.27 (3H, s), 1.49-2.10 (12H, m), 2.85-3.05 (3H, m), 3.70 (1H, m), 4.09 (1H, m), 4.24 (1H, m), 4.27-4.40 (2H, m), 4.83 (1H, m), 7.13-7.34 (5H, m), 7.42 (2X1H, dd, J=8.8Hz), 7.55 (1H, m), 7.80 (2H, br), 7.89 (1H, s), 8.00 (2X1H, dd, J=8 and 1Hz);
MASS (ES+): m/e 595.

Preparation A11

Preparation A11-6

Compound A11-6 was obtained in a manner similar to Preparation A1-6. The obtained compound was used in Preparation C11.

Preparation A12

Preparation A12-2

Compound A12-2 was obtained in a manner similar to Preparations A1-2.

Preparation A12-3

The Compound A12-2 (600 mg) was dissolved in dichloromethane (10 ml), tert-butoxycarbonyl-D-tert-leucine (444 mg), a solution of 1-ethyl-3-(3'-N,N-dimethylaminopropyl)-carbodiimide (328 mg) in dichloromethane (2 ml) and hydroxybenzotriazole (285 mg) were added to the solution, and stirred for 15 hours at ambient temperature. The mixture was washed with 10% aqueous solution of citric acid (10 ml), water (20 ml), saturated sodium bicarbonate (20 ml) and saturated sodium chloride (20 ml), dried over sodium sulfate and the solvent was evaporated to give a crude compound as pale yellow oil. The crude compound was purified by flash column chromatography (Kieselgel 60, 30 g, eluent: ethyl acetate : hexane = 1:2 to 1:1) to give Compound A12-3 (669 mg) as a white foam.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.60 (9x1/3H, s), 0.74 (9x2/3H, s), 1.36 (9x1/3H, s), 1.38 (9x2/3H, s), 1.64-2.30 (4H, m), 2.75-2.89 (1+1/3H, m), 2.93 (1x2/3H, dd, J=13.5 and 6.5Hz), 3.16-3.72 (2H, m), 3.84 (1x1/3H, d, J=10Hz), 3.90 (1x2/3H, d, J=10Hz), 4.17 (1x2/3H, dd, J=8,4Hz), 4.38 (1x1/3H, m), 4.80 (1x2/3H, m), 5.10 (1x1/3H, m), 6.40 (1x1/3H, d, J=10Hz), 6.47 (1x2/3H, d, J=10Hz), 7.12-7.30 (5H, m), 8.31 (1x2/3H, d, J=8Hz), 8.65 (1x1/3H, d, J=8Hz);

MASS (ES+): m/e 490.

Preparation A12-4

The Compound A12-3 (297 mg) was dissolved in dioxane (3 ml) and cold solution of 4N hydrogen chloride in dioxane (3 ml) was added to the mixture and stirred for 12 hours at ambient temperature. The mixture was evaporated to dryness to give Compound 1 (250 mg) as a white powder.

^{1}H-NMR (300MHz, DMSO-d_6 δ): 0.63 (9x1/3H, s), 0.82 (9x2/3H, s), 1.60-2.30 (4H, m), 2.79-2.92 (1+1/3H, m), 2.97 (1x2/3H, dd, J=13 and 7Hz), 3.05-3.66 (3H, m), 3.61 (3x2/3H, s), 3.75 (3x1/3H, s), 4.21 (1x2/3H, dd, J=8.5, 3.5Hz), 4.55 (1x1/3H, m), 4.94 (1x2/3H, ddd, J=8, 8, 7Hz), 5.14 (1x1/3H, dd, J=8, 4Hz), 7.12-7.33 (5H, m), 8.10 (2H, br), 8.80 (1x2/3H, d, J=8Hz), 9.03 (1x1/3H, d, J=8Hz);
MASS (ES+): m/e 390.

The Compound 1 (227 mg) was dissolved in dichloromethane (3 ml) and a solution of Compound c (217 mg) in dichloromethane (2 ml), hydroxybenzotriazole (86.4 mg) and a solution of 1-ethyl-3-(3'-N,N-dimethylaminopropyl)carbodiimide (99.3 mg) in dichloromethane (3 ml) were added to the solution, and the mixture was stirred for 15 hours at ambient temperature. The mixture was washed with 10% aqueous solution of citric acid (20 ml), saturated sodium bicarbonate (20 ml) and saturated sodium chloride (20 ml), dried over sodium sulfate and the solvent was evaporated to give a crude compound. The crude compound was purified by preparative thin layer chromatography (Merck Art 5717 x 2 plates, eluent: ethyl acetate : hexane = 1:1) to give Compound A12-4 (297 mg) as a white foam.

^{1}H-NMR (300MHz, DMSO-d_6 δ): 0.55 (9X1/3H, s), 0.70 (9X2/3H, s), 1.10-1.90 (10H, m), 1.22 (3H, d, J=7Hz), 1.36 (9H, s), 1.93-2.33 (2H, m), 2.40-2.60 (2H, m), 2.71-2.89 (1+1/3H, m), 2.94 (1X2/3H, dd, J=13.7Hz), 3.18-3.73 (2H, m), 3.53 (3X2/3H, s), 3.74 (3X1/3H, s), 3.95 (1H, m), 3.97 (1H, q, J=7Hz), 4.16 (1X2/3H, dd, J=8.4Hz), 4.23 (1X1/3H, d, J=10Hz), 4.28 (1X2/3H, d, J=10Hz), 4.45 (1H, d, J=12Hz), 4.49 (1H, d, J=12Hz), 4.82 (1H, m), 5.14 (1X1/3H, m), 6.91 (1X1/3H, m), 6.91 (1X1/3H, d, J-7Hz), 6.95 (1X2/3H, d, J=7Hz), 7.11-7.40 (10H, m), 7.49 (1X1/3H, d, J=10Hz), 7.52 (1X2/3H, d, J=10Hz), 8.50 (1X2/3H, d, J=8Hz), 8.82 (1X1/3H, d, J-8Hz);
MASS (ES-): m/e 777.

Preparation A12-5

Compound A12-5 was obtained in a manner similar to Preparation A1-5 except that 1N sodium hydroxide aqueous solution was used instead of the hydrogenation catalyst.

^{1}H-NMR (300MHz, DMSO-d_6, δ): 0.52 (9X5/9H, s), 0.72 (9X4/9H, s), 1.10-1.90 (10H, m), 1.22 (3H, d, J=7Hz), 1.35 (9X5/9H, s), 1.37 (9X4/9H, s), 2.15 (2H, m), 2.42-2.60 (2H, m), 2.70-3.00 (2H, m), 3.08-3.65 (2H, m), 3.95 (1H, m), 3.96 (1H, q, J=7Hz), 4.10 (1X4/9H, dd, J=8 and 4Hz), 4.24 (1X5/9H, d, J=10Hz), 4.27 (1X4/9H, d, J=10Hz), 4.38 (1X4/9H, m), 4.45 (1H, d, J=12Hz), 4.49 (1H, d, J=12Hz), 4.83 (1X5/9H, m), 5.02 (1X5/9H, m), 6.91 (1X5/9H, d, J=7.5Hz), 6.95 (1X4/9H, d, J=7.5Hz), 7.10-7.40 (10H, m), 7.48 (1X5/9H, brd, J=10Hz), 7.51 (1X4/9H, brd, J=19Hz), 8.41 (1X4/9H, d, J=8Hz), 8.79 (1X5/9H, d, J=8Hz);
MASS (ES-): m/e 763.

Preparation A12-6

Compound A12-6 was obtained in a manner similar to Preparation A1-6. The obtained compound was used in Preparation C12.

^{1}H-NMR (300MHz, DMSO-d_6, δ): 0.52 (9x1/2H, s), 0.73 (9x1/2H, s), 1.10-1.50 (4H, m), 1.21 (3x1/2H, d, J=6.5Hz), 1.22 (3x1/2H, d, J=6.5Hz), 1.58-1.96 (6H, m), 2.12-2.29 (2H, m), 2.35-2.60 (2H, m), 2.70-3.00 (2H, m), 3.06-3.66 (2H, m), 3.95 (1H, m), 3.96 (1x1/2H, q, J=6.5Hz), 3.97 (1x1/2H, q, J=6.5Hz), 4.10 (1x1/2H, m), 4.26-4.54 (3+1/2H, m), 4.85 (1x1/2H, m), 5.06 (1x1/2H, m), 7.14-7.41 (10H, m), 8.09 (2H, br), 8.55 (1x1/2H, d, J=8.5Hz), 8.60 (1x1/2H, d, J=9Hz), 8.67 (1x1/2H, d, J=8Hz), 8.88 (1x1/2H, d, J=7Hz);
MASS (ES-): m/e 663.

Preparation B

Preparation B1

Preparation B1-1

2-Chlorotrityl chloride resin (Nova Biochem, 0.9 mmol Cl/gram, 2.0 g) was washed with dichloromethane (3 ml) for 5 minutes twice. The resin was suspended in dichloromethane (3 ml) and to the suspension were added N-(9-fluorenylmethoxycarbonyl)-(R)-proline (1.82 g) in dichloromethane (3 ml) and N,N-diisopropylethylamine (698 mg). The suspension was shaken using rotary shaker for 15 minutes. Additionally, N,N-diisopropylethylamine (1.05 g) was added to the suspension and

the mixture was shaken for 1 hour. The reagents and solvent were washed away and the residual solid was washed with dichloromethane (20 ml, 5 times), N,N-dimethylformamide (20 ml, 3 times), dichloromethane (20 ml, 3 times) and isopropyl alcohol (20 ml). The resulting solid was dried under vacuum to give Compound B1-1 (2.89 g).

To determine the loading value, the Compound B1-1 (300 mg) was treated with a mixture of dichloromethane-trifluoroacetic acid (1:1 v/v, 6 ml) for 1 hour. The Compound B1-1 was filtered and the filtrate was concentrated in vacuo to give 107 mg of N-(9-fluorenylmethoxycarbonyl)-(R)-proline (107 mg) which was identical with the starting material by HPLC analysis. Mightysil RP-18 GP 250-4.6 (5 mm) (Kanto Chemical Co., Ltd.), 0.1% TFA-acetonitrile/0.1% TFA-water 50:50 rt=12.15 minutes.

^{1}H-NMR (300MHz, DMSO-d_6, δ): 1.78-2.34 (4H, m), 3.32-3.50 (2H, m), 4.11-4.37 (4H, m), 7.10-7.38 (3H, m), 7.43 (2H, t, J=7.7Hz), 7.62-7.71 (2H, m), 7.90 (2H, dd, J=7.8 and 4.1Hz).

Preparation B1-2

A solution of piperidine in N,N-dimethylformamide (20% v/v, 20 ml) was added to the Compound B1-1 (2.00 g) and the resulting suspension was shaken using rotary shaker for 15 minutes. The suspension was filtered and then a solution of piperidine in N,N-dimethylformamide (20% v/v, 20 ml) was added to the residual solid. The suspension was shaken for additional 15 minutes. The suspension was filtered and the residual solid was washed with N,N-dimethylformamide (20 ml, 5 times). To the residual solid were added (S)-N-(9-fluorenylmethoxycarbonyl)phenylalanine (2.46 g), benzotriazole-1-yloxy-tris-pyrrolidinophosphonium hexafluorophosphate (PyBOP®; 3.31 g) and N,N-diisopropylethylamine (822 mg) at ambient temperature and the resulting suspension was shaken at the same temperature for 16 hours. The suspension was filtered and the residual solid was washed with N,N-dimethylformamide (20 ml, 5 times), dichloromethane (20 ml, 3 times) and isopropyl alcohol, and dried to give Compound B1-2 (2.08 g).

To determine the loading value, the Compound B1-2 (200 mg) was treated with a mixture of dichloromethane-trifluoroacetic acid (1:1 v/v, 4 ml) for 1 hour. The Compound B1-2 was filtered and the filtrate was concentrated in vacuo to give a dipeptide

compound (79 mg). The purity of the dipeptide compound was determined by HPLC analysis. Mightysil RP-18 GP 250-4.6 (5mm) (Kanto Chemical Co., Ltd.), 0.1% TFA-acetonitrile/0.1% TFA-water 50:50 rt=20.64 minutes.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.50-1.71 (2H, m), 1.74-1.91 (1H, m), 2.16-2,34 (1H, m), 3.00 (1H, dd, J=12.5 and 9.6Hz), 3.12 (1H, dd, J=12.5 and 5.7Hz), 3.49-3.62 (1H, m), 4.21 (1H, t, J=6.6Hz), 4.38 (2H, d, J=6.6Hz), 4.65-4,80 (1H, m), 5.71 (1H, d, J=9.2Hz), 7.12-7.46 (9H, m), 7.59 (2H, t, J=7.0Hz), 7.77 (2H, d, J=7.4Hz); MASS (ES+): m/e 485.13 (M+1).

Preparation B1-3

A solution of piperidine in N,N-dimethylformamide (20% v/v, 20 ml) was added to the Compound B1-2 (1.6 g), and the resulting suspension was shaken using rotary shaker for 15 minutes. The suspension was filtered and then 20% N,N-dimethylformamide solution of piperidine (15 ml) was added to the residual solid and the suspension was shaken for additional 15 minutes. The suspension was filtered and the residual solid was washed with N,N-dimethylformamide (20 ml, 3 times). To the solid were added (S)-6-benzoyloxy-2-N-tert-butoxycarbonylaminohexanoic acid (1.53 g), benzotriazole-1-yloxy-tris-pyrrolidinephoponium hexafluorophosphate (PyBOP®; 2.34 g) and N,N-diisopropylethylamine (581 mg) at ambient temperature and the resulting suspension was shaken at the same temperature for 16 hours. The suspension was filtered and the residual solid was washed with N,N-dimethylformamide (10 ml, twice), isopropyl alcohol (10 ml), dichloromethane (10 ml, twice). This washing cycle was repeated once and then the solid was washed with isopropyl alcohol (10 ml) and diethyl ether (10 ml) successively, and dried to give Compound B1-3 (1.80 g).

To determine the loading value, the Compound B1-3 (300 mg) was treated with a mixture of dichloromethane-trifluoroacetic acid (1:1 v/v, 4 ml) for 1 hour. The Compound B1-3 was filtered and the filtrate was concentrated in vacuo and the residual solvent was removed azeotropically with toluene to give a tripeptide compound. The purity of the tripeptide compound was determined by HPLC analysis. Mightysil RP-18 GP 250-4.6 (5 mm) (Kanto chemical Co., Ltd.), 0.1% TFA-acetonitrile/0.1% TFA-water 40:60 rt=7.76 minutes.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.66-0.83 (3H, m), 1.19-2.38 (9H, m), 2.68-2.85 (1H, m), 2.91-3.12 (2H, m), 3.58-3.74 (1H, m), 4.11-4.25 (1H, m), 4.30-4.46 (3H, m), 4.98 (1H, br.s), 5.71 (1H, br. s), 7.11-7.52 (10H, m), 7.60 (2H, d, J=6.9Hz), 7.76 (2H, d, J=7.3Hz);
MASS (ES+): m/e 584.39 (M+1).

Preparation B1-4

A solution of piperidine in N,N-dimethylformamide (20% v/v, 100 ml) was added to the Compound B1-3 (1.15 g) and the suspension was shaken using rotary shaker for 15 minutes. The suspension was filtered, then a solution of piperidine in N,N-dimethylformamide (20% v/v, 100 ml) was added to the residual solid, and the suspension was shaken for additional 15 minutes. The suspension was filtered and washed with N,N-dimethylformamide (15 ml, 5 times). To the residual solid were added Compound b (1.15 g), benzotriazole-1-yloxy-tris-pyrrolidinephoponium hexafluorophosphate (PyBOP®; 1.69 g) and N,N-diisopropylethylamine (420 mg) at ambient temperature and the resulting suspension was shaken at the same temperature for 36 hours. The suspension was filtered and the residual solid was washed with N,N-dimethylformamide (10 ml, twice), isopropyl alcohol (10 ml), dichloromethane (10 ml, twice). This washing cycle was repeated and then the residual solid was washed with isopropyl alcohol (10 ml) and diethyl ether (20 ml) successively to give Compound B1-4 (300 mg).

Preparation B1-5

The Compound B1-4 (300 mg) was treated with a mixture of dichloromethane-trifluoroacetic acid (1:1 v/v, 6 ml) for 1 hour. The suspension was filtered and the filtrate was concentrated in vacuo to give Compound B1-5 (128 mg). The purity of the Compound B1-5 was determined by HPLC analysis. Mightysil RP-18 GP 250-4.6 (5 mm) (Kanto chemical Co., Ltd.), 0.1% TFA-acetonitrile/0.1% TFA-water 40:60 rt=7.76 minutes. The Compound B1-5 was used in Preparation C10.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.69 (3H, t, J=6.8Hz), 1.28 (3H, s), 1.46-1.70 (3H, m), 1.71-2.08 (9H, m), 2.84-3.04 (3H, m), 3.63-3.78 (1H, m), 4.04-4.15 (1H, m), 4.20-4.38 (3H, m), 4.79-4.90 (1H, m), 7.11-7.32 (6H, m), 7.41 (2H, t, J=8.1Hz), 7.45-7.62 (2H, m), 7.73-8.14 (5H, m);

MASS (ES+); m/e 595.21 (M+1).

Preparation B2

Preparation B2-4

Compound B2-4 was obtained in a manner similar to Preparations B1-4.

Preparation B2-5

Compound B2-5 was obtained in a manner similar to Preparation B1-5. The obtained compound was used in Preparation C8.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.67 (3H, t, J=7.3Hz), 1.29 (3H, s), 1.51-1.63 (2H, m), 1.63-2.06 (10H, m), 2.36 (3H, s), 2.83-3.0 (2H, m), 3.0-3.15 (1H, m), 3.68-3.78 (1H, m), 4.0-4.10 (1H, m), 4.26-4.40 (3H, m), 4.84 (1H, m), 5.20-5.45 (1H, brs), 7.10-7.32 (4H, m), 7.41 (2H, t, J=7.6Hz), 7.52 (1H, t, J=7.3Hz), 7.66 (1H, brd, J=3.3Hz), 7.80-8.10 (1H, brs), 7.99 (2H, d, J=6.9Hz).

Preparation B3

Preparation B3-5

Compound B3-5 was obtained in a manner similar to Preparation B1-5. The obtained compound was used in Preparation C3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.69 (3H, t, J=7.3Hz), 1.32 (3H, s), 1.46-2.24 (12H, m), 2.81-3.11 (3H, m), 3.65-3.79 (1H, m), 3.97-4.58 (4H, m), 4.82-4.95 (1H, m), 6.95 (2H, t, J=8.8Hz), 7.11-7.31 (4H, m), 7.36-7.82 (4H, m), 7.99 (2H, d, J=7.0Hz), 8.04 (1H, br.s);

MASS (ES+): m/e 613.21 (M+1, free).

Preparation B4

Preparation B4-5

Compound B4-5 was obtained in a manner similar to Preparations B1-5. The obtained compound was used in Preparation C12.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.70 (3H, t, J=7.4Hz), 1.29 (3H, s), 1.44-2.11 (12H, m), 2.80-3.03 (3H, m), 3.63-3.78 (1H, m), 3.76 (3H, s), 4.02-4.46 (4H, m), 4.75-4.88 (1H, m), 6.79 (2H, d, J=8.3Hz), 7.09 (2H, d, J=8.3Hz), 7.14-7.31 (2H, m), 7.36-7.80 (4H, m), 8.00 (2H, d, J=7.4Hz), 8.13 (1H, br. s);

MASS (ES+): m/e 625.28 (M+1, free).

Preparation B5

Preparation B5-5

Compound B5-5 was obtained in a manner similar to Preparations B1-5. The obtained compound was used in Preparation C11.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.58-0.94 (6H, m), 0.95-1.33 (2H, m), 1.49-2.16 (16H, m), 3.00 (2H, br. d, J=8.1Hz), 3.03-3.18 (1H, m), 3.68-3.87 (1H, m), 4.02-4.16 (1H, m), 4.19-4.38 (3H, m), 4.67-4.83 (1H, m), 4.73-5.16 (2H, m), 7.11-7.35 (5H, m), 7.36-7.84 (4H, m), 7.94-8.19 (1H, br. s), 7.97-8.04 (2H, m);
MASS (ES+): m/e 637.23 (M+1, free).

Preparation B6

Preparation B6-5

Compound B6-5 was obtained in a manner similar to Preparations B1-5. The obtained compound was used in Preparation C9.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.48 (3H, t, J=7.3Hz), 0.64 (3H, t, J=7.2Hz), 0.72-0.91 (2H, m), 1.52-2.17 (12H, m), 2.91-3.11 (3H, m), 3.70-3.83 (1H, m), 3.97-4.43 (4H, m), 4.74-5.03 (1H, m), 7.13-7.34 (5H, m), 7.37-7.72 (4H, m), 7.76-7.84 (1H, m), 7.95-8.18 (2H, m), 7.97-8.04 (2H, m).

Preparation C

Preparation C1

Preparation C1-1

To a stirred solution of benzotriazol-1-yl-oxy-tris-(N,N-dimethylamino)phosphoniumhexafluorophosphate (23.9 g) and 4-(N,N-dimethylamino)pyridine (7.6 g) in dry N,N-dimethylformamide (1.5 L), the Compound A1-6 (4.64 g) in dry N,N-dimethylformamide (8 ml) was added dropwise over 20 hours at room temperature. The volatiles were removed under reduced pressure and the residue was diluted with ethyl acetate (300 ml). The precipitate formed was collected by filtration, dissolved in ethyl acetate (50 ml), then washed with 5% aqueous potassium hydrogen sulfate solution (100 ml, 4 times), saturated aqueous sodium bicarbonate solution (100 ml, 3 times), water (100 ml) and brine (100 ml). The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluted with ethyl acetate/hexane = 1:1 v/v) to give Compound C1-1 (3.083 g) as a colorless amorphous.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.0Hz), 1.28 (3H, s),

1.36-1.55 (2H, m), 1.59-1.99 (4H, m), 2.04-2.24 (2H, m), 2.24-2.40 (2H, m), 2.90 (1H, dd, J=13.6, 6.6Hz), 3.19 (1H, dd, J=13.6, 9.9Hz), 3.20-3.31 (1H, m), 3.80-3.91 (1H, m), 4.18-4.28 (1H, m), 4.32 (2H, t, J=6.2Hz), 4.67 (1H, br.d, J=5.5Hz), 5.03 (2H, s), 5.14 (1H, dt, J=10 and 5.6Hz), 5.85 (1H, s), 6.89 (2H, d, J=8.6Hz), 7.14 (1H, s), 7.15 (2H, d, J=8.6Hz), 7.28-7.48 (9H, m), 7.49-7.60 (2H, m), 8.00-8.06 (2H, m);
MASS (ES+): m/e 683.49 (M+1).

Preparation C1-2

To a stirred solution of the Compound C1-1 (3.07 g) in methanol (30 ml) was added 1N aqueous sodium hydroxide solution (11.2 ml, 2.5 eq) under ice-cooling and the mixture was stirred at ambient temperature for 4 hours. The pH of the mixture was adjusted to pH 7 with 1N hydrogen chloride, then methanol was evaporated under reduced pressure. The residue was extracted with ethyl acetate (300 ml). The organic layer was washed with saturated aqueous ammonium chloride (50 ml, twice), water (50 ml) and brine (50 ml), dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (ethyl acetate, then methanol/ethyl acetate = 5:95 v/v) to give Compound C1-2 (2.63 g) as a colorless amorphous solid.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.4Hz), 1.28 (3H, s), 1.20-1.92 (8H, m), 2,07-2.23 (2H, m), 2,24-2,39 (2H ,m), 2.89 (1H, dd, J=13.8 and 6.1Hz), 3.18 (1H, dd, J=13.8 and 9.5Hz), 3.15-3.28 (1H. m), 3.65 (2H, d, J=6.5Hz), 3.78-3.91 (1H, m), 4.15-4.28 (1H, m), 4.67 (1H, br.d, J=5.8Hz), 5.03 (2H ,s), 5.13 (1H, dt, J=9.5 and 6.2Hz), 5.93 (1H, s), 6.88 (2H, d, J=8.5Hz), 7.11-7.15 (1H, m), 7.14 (2H, d, J=8.5Hz), 7.27-7.45 (5H, m), 7.52 (1H, d, J=10.2Hz);
MASS (ES+): m/e 579.30 (M+1).

Preparation C1-3

To a stirred solution of the Compound C1-2 (1.0 g) in dichloromethane (50 ml) was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (3.66 g) in one portion under ice-cooling. The mixture was stirred at ambient temperature for 2 hours. The reaction was quenched with a solution of 20% sodium thiosulfate in saturated sodium hydrogen carbonate (100 ml) under ice-cooling, then the mixture was

extracted with ethyl acetate (100 ml), washed with saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate, and evaporated in vacuo to give Compound C1-3 as a colorless amorphous (980 mg). The obtained compound was used in Example 1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.3Hz), 1.30 (3H, s), 1.50-1.91 (6H, m), 2.08-2.38 (4H, m), 2.46-2.55 (2H, br.t, J=6.8Hz), 2.90 (1H, dd, J=13.7 and 5.9Hz), 3.18 (1H, dd, J=13.7 and 7.3Hz), 3.20-3.30 (1H, m), 3.80-3.91 (1H, m), 4.17-4.29 (1H, m), 4.68 (1H, br.d, J=6.3Hz), 5.03 (2H, s), 5.14 (1H, dt, J=9.5 and 5.6Hz), 5.90 (1H, s), 6.89 (2H ,d, J=8.5Hz), 7.10-7.21 (1H, m), 7.14 (2H, d, J=8.5Hz), 7.22-7.45 (5H, m), 7.47 (1H, d, J=10.3Hz), 9.77 (1H, s);

MASS (ES+): m/e 577.25 (M+1).

Preparation C2

Preparation C2-1

Compound C2-1 was obtained in a manner similar to Preparation C1-1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.28 (3H, s), 1.46 (2H, m), 1.60-1.98 (6H, m), 2.06-2.40 (4H, m), 2.90 (1H, dd, J=14 and 6Hz), 3.18 (1H, dd, J=14 and 10Hz), 3.26 (1H, m), 3.77 (3H, s), 3.86 (1H, m), 4.24 (1H, m), 4.32 (2H, t, J=6.5Hz), 4.67 (1H, m), 5.14 (1H, ddd, J=10, 10 and 6Hz), 5.85 (1H, s), 6.81 (2x1H, d, J=9Hz), 7.14 (2x1H, d, J=9Hz), 7.14 (1H, d, J=10Hz), 7.44 (2x1H, dd, J=7.5 and 7.5Hz), 7.50-7.60 (2H, m), 8.03 (2x1H, d, J=7.5Hz);

MASS (ES-): m/e 605.

Preparation C2-2

Compound C2-2 was obtained in a manner similar to Preparation C1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.3Hz), 1.25-1.51 (2H, m), 1.28 (3H, s), 1.54-1.94 (6H, m), 2.08-2.40 (4H, m), 2.89 (1H, dd, J=13.5 and 6Hz), 3.18 (1H, dd, J=13.5 and 10Hz), 3.25 (1H, m), 3.65 (2H, m), 3.77 (3H, s), 3.85 (1H, m), 4.22 (1H, dt, J=10 and 7.5Hz), 4.67 (1H, m), 5.13 (1H, ddd, J=10, 10 and 6Hz), 5.99 (1H, s), 6.81 (2x1H, d, J=8.7Hz), 7.14 (2x1H, d, J=8.7Hz), 7.15 (1H, d, J=10Hz), 7.53 (1H, d, J=10Hz);

MASS (ES-): m/e 501.

Preparation C2-3

Compound C2-3 was obtained in a manner similar to Preparation C1-3. The obtained compound was used in Example 2.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.85 (3H, t, J=7.3Hz), 1.29 (3H, s), 1.53-1.90 (6H, m), 2.08-2.37 (4H, m), 2.50 (2H, m), 2.89 (1H, dd, J=14 and 6Hz), 3.17 (1H, dd, J=14 and 10Hz), 3.25 (1H, m), 3.86 (1H, m), 4.23 (1H, m), 4.67 (1H, m), 5.13 (1H, ddd, J=10, 10 and 6Hz), 5.89 (1H, s), 6.81 (2x1H, d, J=8.8Hz), 7.14 (2x1H, d, J=8.8Hz), 7.16 (1H, d, J=11Hz), 7.48 (1H, d, J=10Hz), 9.77 (1H, t, J=1.4Hz);
MASS (ES-): m/e 499.

Preparation C3

Preparation C3-1

Compound C3-1 was obtained in a manner similar to Preparation C1-1.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.81 (3H, t, J=7.3Hz), 1.27 (3H, s), 1.35-1.98 (8H, m), 2.06-2.40 (4H, m), 2.93 (1H, dd, J=13.6, 6.8Hz), 3.20 (1H, dd, J=13.6 and 9.6Hz), 3.21-3.33 (1H, m), 3.78-3.90 (1H, m), 4.18-4.30 (1H, m), 4.32 (2H, t, J=6.4Hz), 4.68 (1H, br. d, J=7.7Hz), 5.07-5.20 (1H, m), 5.84 (1H, s), 6.96 (2H, t, J=8.6Hz), 7.10 (1H, d, J=10.3Hz), 7.19 (1H, dd, J=8.6 and 5.5Hz), 7.44 (2H, t, J=7.3Hz), 7.52-7.61 (2H, m), 8.03 (2H, d, J=8.4Hz);
MASS (ES+): m/e 595.39 (M+1).

Preparation C3-2

Compound C3-2 was obtained in a manner similar to Preparation C1-2.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.3Hz), 1.23-1.95 (8H, m), 1.29 (3H, s), 2.08-2.41 (4H, m), 2.94 (1H, dd, J=13.6 and 6.2Hz), 3.21 (1H, dd, J=13.6 and 9.6Hz), 3.23-3.33 (1H, m), 3.67 (2H, br. t, J=6.2Hz), 3.80-3.91 (1H, m), 4.16-4.30 (1H, m), 4.69 (1H br. d, J=5.5Hz), 5.07-5.20 (1H, m), 5.97 (1H, s), 6.97 (2H, t, J=8.5Hz), 7.11 (1H, d, J=10.2Hz), 7.20 (2H, dd, J=8.5 and 5.1Hz), 7.57 (1H, d, J=10.2Hz);
MASS (ES+): m/e 491.45 (M+1).

Preparation C3-3

Compound C3-3 was obtained in a manner similar to Preparation C1-3. The obtained compound was used in Example 3.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=6.9Hz), 1.29 (3H, s), 1.53-1.90 (6H, m), 2.08-2.38 (4H, m), 2.50 (2H, br. t, J=7.0Hz), 2.93 (1H, dd, J=13.9 and 6.2Hz), 3.19 (1H, dd, J=13.9 and 9.1Hz),

3.20-3.31 (1H, m), 3.79-3.90 (1H, m), 4.17-4.28 (1H, m), 4.68 (1H, br. d, J=6.0Hz), 5.07-5.19 (1H, m), 5.87 (1H, s), 6.96 (2H, t, J=8.9Hz), 7.10 (1H, d, J=10.1Hz), 7.19 (2H, dd, J=8.9 and 5.5Hz), 7.50 (1H, d, J=10.3Hz), 9.77 (1H, s);
MASS (ES+): m/e 489.42 (M+1).

Preparation C4

Preparation C4-1

Compound C4-1 was obtained in a manner similar to Preparation C1-1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.31-1.96 (14H, m), 2.08-2.23 (1H, m), 2.24-2.37 (2H, m), 2.43-2.56 (2H, m), 2.95 (1H, dd, J=13.5 and 5.7Hz), 3.14-3.28 (1H, m), 3.26 (1H, dd, J=13.5 and 10.5Hz), 3.84-3.95 (1H, m), 4.23 (1H, dt, J=10.2 and 7.8Hz), 4.31 (2H, t, J=6.6Hz), 4.63-4.69 (1H, m), 5.15 (1H, ddd, J=10.2, 10.2 and 6.0Hz), 6.13 (1H, s), 7.16-7.31 (6H, m), 7.39-7.48 (3H, m), 7.52-7.60 (1H, m), 8.00-8.05 (2H, m);
MASS (ES+): m/e 589.40 (M+1).

Preparation C4-2

Compound C4-2 was obtained in a manner similar to Preparation C1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.20-1.81 (14H, m), 2.10-2.22 (1H, m), 2.25-2.37 (2H, m), 2.43-2.58 (2H, m), 2.95 (1H, dd, J=13.5 and 5.7Hz), 3.13-3.28 (1H, m), 3.25 (1H, dd, J=13.5 and 10.2Hz), 3.65 (2H, t, J=6.3Hz), 3.85-3.95 (1H, m), 4.22 (1H, dt, J=10.2 and 7.2Hz), 4.67 (1H, dd, J=7.8 and 2.1Hz), 5.15 (1H, ddd, J=10.2, 10.2 and 6.0Hz), 6.28 (1H, s), 7.16-7.31 (6H, m), 7.44 (1H, d, J=10.2Hz);
MASS (ES+): m/e 485.39 (M+1).

Preparation C4-3

Compound C4-3 was obtained in a manner similar to Preparation C1-3. The obtained compound was used in Example 4.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.42-1.92 (13H, m), 2.08-2.22 (1H, m), 2.23-2.37 (2H, m), 2.42-2.56 (2H, m), 2.95 (1H, dd, J=13.8 and 5.7Hz), 3.13-3.28 (1H, m), 3.25 (1H, dd, J=13.8 and 10.2Hz), 3.85-3.95 (1H, m), 4.22 (1H, dt, J=10.2 and 7.2Hz), 4.64-4.69 (1H, m), 5.15 (1H, ddd, J=9.9, 9.9 and 5.7Hz), 6.15 (1H, s), 7.17-7.31 (6H, m), 7.44 (1H, d, J=10.2Hz), 9.77 (1H, s);
MASS (ES+): m/e 483.36 (M+1).

Preparation C5

Preparation C5-1

Compound C5-1 was obtained in a manner similar to Preparation C1-1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.790 (3H, t, J=7.2Hz), 1.27 (3H, s), 1.38-1.98 (8H, m), 2.07-2.38 (4H, m), 3.06 (1H, dd, J=14.1 and 6.9Hz), 3.28-3.36 (1H, m), 3.26 (1H, dd, J=14.1 and 8.4Hz), 3.79-3.89 (1H, m), 4.25 (1H, dt, J=10.2 and 7.8Hz), 4.32 (2H, t, J=6.3Hz), 4.65-4.71 (1H, m), 5.17 (1H, dt, J=9.0 and 6.9Hz), 5.89 (1H, s), 7.01 (1H, d, J=10.2Hz), 7.32-7.38 (2H, m), 7.40-7.48 (2H, m), 7.52-7.63 (3H, m), 7.61-7.67 (1H, m), 8.00-8.06 (2H, m);
MASS (ES+): m/e 602.47 (M+1).

Preparation C5-2

Compound C5-2 was obtained in a manner similar to Preparation C1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.809 (3H, t, J=7.2Hz), 1.24-1.94 (9H, m), 1.28 (3H, s), 2.06-2.41 (4H, m), 3.06 (1H, dd, J=9.0 and 6.9Hz), 3.26-3.36 (1H, m), 3.26 (1H, dd, J=13.5 and 9.0Hz), 3.66 (2H, t, J=6.3Hz), 3.79-3.90 (1H, m), 4.24 (1H, dt, J=10.2 and 7.8Hz), 4.65-4.72 (1H, m), 5.18 (1H, dt, J=9.0 and 7.2Hz), 6.01 (1H, s), 7.02 (1H, d, J=10.2Hz), 7.35 (2H, d, J=8.1Hz), 7.58 (2H, d, J=8.1Hz), 7.64 (1H, d, J=10.2Hz);
MASS (ES+): m/e 498.41 (M+1).

Preparation C5-3

Compound C5-3 was obtained in a manner similar to Preparation C1-3. The obtained compound was used in Example 5.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.812 (3H, t, J=7.2Hz), 1.29 (3H, s), 1.49-1.92 (6H, m), 2.07-2.40 (4H, m), 2.51 (2H, t, J=7.2Hz), 3.06 (1H, dd, J=13.5 and 6.9Hz), 3.26-3.36 (1H, m), 3.26 (1H, dd, J=13.5 and 8.7Hz), 3.78-3.90 (1H, m), 4.24 (1H, dt, J=10.2 and 7.2Hz), 4.65-4.71 (1H, m), 5.18 (1H, dt, J=9.0 and 8.4Hz), 5.93 (1H, s), 7.02 (1H, d, J=10.2Hz), 7.35 (2H, d, J=8.7Hz), 7.57-7.59 (1H, m), 7.58 (2H, d, J=8.8Hz), 9.77 (1H, s);
MASS (ES+): m/e 496.46 (M+1).

Preparation C6

Preparation C6-1

Compound C6-1 was obtained in a manner similar to Preparation C1-1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.82 (3H, t, J=7.5Hz), 1.27 (3H, s),

1.39 (3H, t, J=7.2Hz), 1.40-1.52 (2H, m), 1.64-1.98 (6H, m), 2.06-2.39 (4H, m), 2.88 (1H, dd, J=13.5 and 5.7Hz), 3.09-3.32 (2H, m), 3.79-3.90 (1H, m), 3.99 (2H, q, J=7.2Hz), 4.18-4.30 (1H, m), 4.31 (2H, t, J=6.0Hz), 4.62-4.69 (1H, m), 5.07-5.18 (1H, dt, J=9.9 and 6.0Hz), 5.82 (1H, s), 6.79 (2H, d, J=8.4Hz), 7.10-7.18 (1H, m), 7.13 (2H, d, J=8.4Hz), 7.38-7.59 (4H, m), 7.99-8.05 (2H, m);

MASS (ES+): m/e 621.55 (M+1).

Preparation C6-2

Compound C6-2 was obtained in a manner similar to Prepararion C1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.2Hz), 1.28-1.93 (8H, m), 1.28 (3H, s), 1.39 (3H, t, J=6.9Hz), 2.08-2.23 (2H, m), 2.24-2.39 (2H, m), 2.88 (1H, dd, J=13.5 and 6.0Hz), 3.17 (1H, dd, J=13.5 and 9.9Hz), 3.20-3.30 (1H, m), 3.65 (2H, t, J=6.6Hz), 3.80-3.90 (1H, m), 3.99 (2H, q, J=6.9Hz), 4.22 (1H, dt, J=10.2 and 7.8Hz), 4.64-4.69 (1H, m), 5.13 (1H, dt, J=9.9 and 6.0Hz), 5.93 (1H, s), 6.79 (2H, d, J=8.4Hz), 7.10-7.17 (1H, m), 7.13 (2H, d, J=8.4Hz), 7.52 (1H, d, J=10.2Hz);

MASS (ES+): m/e 517.44 (M+1).

Preparation C6-3

Compound C6-3 was obtained in a manner similar to Preparation C1-3. The obtained compound was used in Example 6.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.85 (3H, t, J=7.2Hz), 1.29 (3H, s), 1.40 (3H, t, J=6.9Hz), 1.49-1.92 (6H, m), 2.09-2.24 (2H, m), 2.24-2.39 (2H, m), 2.50 (2H, dt, J=6.3 and 1.2Hz), 2.88 (1H, dd, J=14.1 and 5.7Hz), 3.17 (1H, dd, J=14.1 and 10.2Hz), 3.20-3.30 (1H, m), 3.81-3.90 (1H, m), 3.99 (2H, q, J=6.9Hz), 4.23 (1H, dt, J=10.2 and 7.2Hz), 4.64-4.70 (1H, m), 5.13 (1H, dt, J=10.2, 5.7Hz), 5.85 (1H, s), 6.80 (2H, d, J=8.4Hz), 7.12-7.19 (1H, m), 7.13 (2H, d, J=8.4Hz), 7.46 (1H, d, J=10.2Hz), 9.77 (1H, t, J=1.2Hz);

MASS (ES+): m/e 515.36 (M+1).

Preparation C7

Preparation C7-1

Compound C7-1 was obtained in a manner similar to Preparation C1-1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.78 (3H, t, J=7.5Hz), 1.25 (3H, s), 1.46 (2H, m), 1.58-1.95 (6H, m), 2.07-2.39 (4H, m), 3.11 (1H, dd,

J=14 and 8Hz), 3.16 (1H, dd, J=14 and 8Hz), 3.41 (1H, m), 3.88 (1H, m), 4.24 (1H, m), 4.32 (2H, t, J=6.5Hz), 4.70 (1H, dd, J=8 and 3Hz), 5.24 (1H, ddd, J=10, 8 and 8Hz), 5.80 (1H, s), 6.97-7.31 (5H, m), 7.44 (2H, dd, J=7.5 and 7.5Hz), 7.50-7.60 (2H, m), 8.00-8.06 (2H, m);
MASS (ES+): m/e 595;
MASS (ES-): m/e 593.

Preparation C7-2

Compound C7-2 was obtained in a manner similar to Preparation C1-2.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.79 (3H, t, J=7.5Hz), 1.22-1.51 (2H, m), 1.26 (3H, s), 1.52-1.73 (3H, m), 1.74-1.94 (3H, m), 2.08-2.40 (4H, m), 3.10 (1H, dd, J=15 and 8Hz), 3.15 (1H, dd, J=15 and 8Hz), 3.41 (1H, m), 3.66 (2H, t, J=7Hz), 3.88 (1H, m), 4.23 (1H, m), 4.70 (1H, m), 5.24 (1H, ddd, J=10, 8 and 8Hz), 5.91 (1H, s), 6.97-7.08 (2H, m), 7.10 (1H, d, J=10Hz), 7.15-7.28 (2H, m), 7.54 (1H, d, J=10Hz);
MASS (ES+): m/e 491;
MASS (ES-): m/e 489.

Preparation C7-3

Compound C7-3 was obtained in a manner similar to Preparation C1-3. The obtained compound was used in Example 7.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.80 (3H, t, J=7Hz), 1.26 (3H, s), 1.50-1.94 (6H, m), 2.11-2.44 (4H, m), 2.51 (2H, m), 3.05-3.20 (2H, m), 3.41 (1H, m), 3.89 (1H, m), 4.24 (1H, m), 4.71 (1H, m), 5.24 (1H, m), 5.85 (1H, s), 6.97-7.28 (5H, m), 7.49 (1H, d, J=10Hz), 9.78 (1H, s);
MASS (ES-): m/e 487;
MASS (ES+): m/e 489.

Preparation C8

Preparation C8-1

Compound C8-1 was obtained in a manner similar to Preparation C1-1.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.28 (3H, s), 1.25-1.47 (2H, m), 1.56-1.74 (4H, m), 1.76-1.89 (2H, m), 2.15-2.36 (4H, m), 2.93 (1H, dd, J=13.6 and 6.6Hz), 3.20 (1H, dd, J=13.6 and 9.5Hz), 3.20-3.32 (1H, m), 3.66 (2H, t, J=6.6Hz), 3.85 (1H, ddd, J=13.2, 8.1 and 4.4Hz), 4.22 (1H, ddd, J=15, 7.6 and 2.2Hz), 4.67 (1H, brd, J=5.8Hz), 5.15 (1H, ddd, J=16.5, 9.5 and

6.6Hz), 5.99 (1H, s), 7.08 (1H, d, J=10.6Hz), 7.16 (2H, d, J=8.9Hz), 7.22 (2H, d, J=8.9Hz), 7.58 (1H, d, J=10.3Hz).

Preparation C8-2

Compound C8-2 was obtained in a manner similar to Preparation C1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.81 (3H, t, J=7.3Hz), 1.27 (3H, s), 1.41-1.58 (2H, m), 1.61 (3H, s), 1.71-1.90 (4H, m), 2.05-2.34 (4H, m), 2.95 (1H, dd, J=13.5 and 6.2Hz), 3.20 (1H, dd, J=13.5 and 9.2Hz), 3.25-3.36 (1H, m), 3.82-3.89 (1H, m), 4.25 (1H, dd, J=17.9 and 10.2Hz), 4.32 (2H, t, J=6.2Hz), 4.68 (1H, brd, J=6.6Hz), 5.14 (1H, ddd, J=16.7, 9.5 and 6.6Hz), 5.81 (1H, s), 7.08 (1H, d, J=9.9Hz), 7.16 (2H, d, J=8.1Hz), 7.24 (2H, d, J=8.1Hz), 7.44 (2H, t, J=8.4Hz), 7.56 (1H, dd, J=6.6 and 4.3Hz), 8.03 (2H, d, J=7.3Hz).

Preparation C8-3

Compound C8-3 was obtained in a manner similar to Preparation C1-3. The obtained compound was used in Example 8.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.5Hz), 1.29 (3H, s), 1.52-1.90 (6H, m), 2.08-2.38 (4H, m), 2.50 (2H, m), 2.94 (1H, dd, J=13.5 and 6Hz), 3.19 (1H, dd, J=13.5 and 9.5Hz), 3.28 (1H, m), 3.85 (1H, m), 4.24 (1H, m), 4.68 (1H, m), 5.14 (1H, ddd, J=10, 9.5 and 6Hz), 5.89 (1H, s), 7.09 (1H, d, J=10.5Hz), 7.16 (2X1H, d, J=8.5Hz), 7.25 (2X1H, d, J=8.5Hz), 7.52 (1H, d, J=10Hz), 9.77 (1H, t, J=1.3Hz);

MASS (ES-): m/e 503.

Preparation C9

Preparation C9-1

Compound C9-1 was obtained in a manner similar to Preparation C1-1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.75 (3H, t, J=7.3Hz), 0.91 (3H, t, J=7.3Hz), 1.35-1.98 (10H, m), 2.10-2.43 (4H, m), 2.97 (1H, dd, J=13.5 and 6.4Hz), 3.24 (1H, dd, J=13.5 and 9.4Hz), 3.21-3.30 (1H, m), 3.83-3.94 (1H, m), 4.25 (1H, dt, J=10.3 and 7.6Hz), 4.32 (2H, t, J=6.2Hz), 4.63-4.70 (1H, m), 5.18 (1H, dt, J=10.2 and 6.3Hz), 5.78 (1H, s), 7.13 (1H, d, J=10.3Hz), 7.19-7.32 (5H, m), 7.40-7.47 (2H, m), 7.50 (1H, d, J=10.2Hz), 7.51-7.60 (1H, m), 8.01-8.06 (2H, m);

MASS (ES+): m/e 591.21 (M+1).

Preparation C9-2

Compound C9-2 was obtained in a manner similar to Preparation C1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.77 (3H, t, J=7.7Hz), 0.91 (3H, t, J=7.3Hz), 1.20-1.93 (10H, m), 2.07-2.45 (4H, m), 2.97 (1H, dd, J=13.5 and 6.2Hz), 3.24 (1H, dd, J=13.5 and 9.1Hz), 3.21-3.30 (1H, m), 3.66 (2H, t, J=6.6Hz), 3.82-3.93 (1H, m), 4.24 (1H, dd, J=10.0 and 7.2Hz), 4.67 (1H, br. d, J=8.0Hz), 5.12-5.23 (1H, m), 5.84 (1H, s), 7.12 (1H, d, J=10.0Hz), 17.16-7.31 (5H, m), 7.49 (1H, d, J=10.4Hz);

MASS (ES+): m/e 487.19 (M+1).

Preparation C9-3

Compound C9-3 was obtained in a manner similar to preparation C1-3. The obtained compound was used in Example 9.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.77 (3H, t, J=7.4Hz), 0.91 (3H, t, J=7.4Hz), 1.50-1.92 (8H, m), 2.07-2.42 (4H, m), 2.51 (2H, br. t, J=6.1Hz), 2.96 (1H, dd, J=13.1 and 5.7Hz), 3.17-3.30 (2H, m), 3.83-3.94 (1H, m), 4.18-4.30 (1H, m), 4.67 (1H, br. d, J=6.1Hz), 5.12-5.23 (1H, m), 5.85 (1H, s), 7.15 (1H, d, J=10.8Hz), 7.18-7.31 (5H, m), 7.44 (1H, d, J=10.0Hz), 9.77 (1H, s);

MASS (ES+): m/e 485.29 (M+1).

Preparation C10

Preparation C10-1

Compound C10-1 was obtained in a manner similar to Preparation C1-1 except that benzotriazol-1-yloxy-tris-pyrrolidinephoponium hexafluorophosphate was used instead of benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.81 (3H, t, J=7.3Hz), 1.28 (3H, s), 1.46 (2H, m), 1.61-2.00 (6H, m), 2.06-2.39 (4H, m), 2.97 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 9.5Hz), 3.26 (1H, m), 3.86 (1H, m), 4.24 (1H, m), 4.32 (2H, t, J=6.5Hz), 4.67 (1H, m), 5.18 (1H, m), 5.82 (1H, s), 7.13 (1H, d, J=11Hz), 7.16-7.32 (5H, m), 7.39-7.59 (2H, m), 7.51-7.60 (2H, m), 7.95-8.08 (2H, m);

MASS (ES-): m/e 575.

Preparation C10-2

Compound C10-2 was obtained in a manner similar to Preparation C1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.5Hz), 1.22-1.95 (8H, m), 1.28 (3H, s), 2.07-2.40 (4H, m), 2.96 (1H, dd, J=13 and

6.5Hz), 3.04 (1H, dd, J=13 and 9Hz), 3.06 (1H, m), 3.65 (2H, br-t, J=6Hz), 3.86 (1H, m), 4.23 (1H, m), 4.68 (1H, m), 5.19 (1H, ddd, J=10, 9, 6Hz), 5.93 (1H, s), 7.12 (1H, d, J=11Hz), 7.16-7.32 (5H, m), 7.55 (1H, d, J=10Hz);

MASS (ES-): m/e 471.

Preparation C10-3

Compound C10-3 was obtained in a manner similar to Preparation C1-3. The obtained compound was used in Example 10.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.3Hz), 1.29 (3H, s), 1.48-1.95 (6H, m), 2.06-2.59 (6H, m), 2.97 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 10Hz), 3.26 (1H, m), 3.86 (1H, m), 4.24 (1H, m), 4.68 (1H, dd, J=8 and 2Hz), 5.19 (1H, ddd, J=10, 10 and 6Hz), 5.92 (1H, s), 7.16 (1H, d, J=11Hz), 7.16-7.33 (5H, m), 7.50 (1H, d, J=10Hz), 9.77 (1H, br-s);

MASS (ES-): m/e 469.

Preparation C11

Preparation C11-1

Compound C11-1 was obtained in a manner similar to Preparation C1-1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.87 (3H, t, J=7.2Hz), 0.96 (3H, t, J=7.0Hz), 0.93-1.04 (1H, m), 1.11-1.36 (3H, m), 1.37-1.64 (3H, m), 1.65-1.96 (7H, m), 2.00-2.24 (2H, m), 2.27-2.42 (2H, m), 2.98 (1H, dd, J=13.6 and 6.6Hz), 3.21-3.32 (1H, m), 3.23 (1H, dd, J=13.6 and 9.5Hz), 3.81-3.93 (1H, m), 4.18-4.29 (1H, m), 4.32 (2H, t, J=6.5Hz), 4.67 (1H, br. d, J=7.7Hz), 5.10-5.23 (1H, m), 5.78 (1H, s), 7.13 (1H, d, J=10.2Hz), 7.19-7.32 (5H, m), 7.40-7.60 (4H, m), 8.01-8.06 (2H, m);

MASS (ES+): m/e 619.34 (M+1).

Preparation C11-2

Compound C11-2 was obtained in a manner similar to Preparation C1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.89 (3H, t, J=7.0Hz), 0.96 (3H, t, J=6.8Hz), 0.97-1.08 (1H, m), 1.12-1.92 (13H, m), 2.02-2.26 (2H, m), 2.27-2.44 (2H, m), 2.98 (1H, dd, J=13.5 and 6.6Hz), 3.20-3.31 (1H, m), 3.22 (1H, dd, J=13.5 and 9.6Hz), 3.66 (2H, br. t, J=6.3Hz), 3.82-3.92 (1H, m), 4.22 (1H, dt, J=10.2 and 7.6Hz), 4.67 (1H, br.d, J=7.5Hz), 5.11-5.22 (1H, m), 5.86 (1H, s), 7.12 (1H, d, J=10.3Hz), 7.17-7.31 (5H, m), 7.49 (1H, d, J=10.3Hz);

MASS (ES+): m/e 515.23 (M+1).

Preparation C11-3

Compound C11-3 was obtained in a manner similar to Preparation C1-3. The obtained compound was used in Example 11.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.89 (3H, t, J=6.6Hz), 0.94-1.08 (1H, m), 0.96 (3H, t, J=6.9Hz), 1.10-1.38 (4H, m), 1.43-1.92 (6H, m), 2.00-2.42 (5H, m), 2.50 (2H, br. t, J=6.6Hz), 2.98 (1H, dd J=13.5 and 6.6Hz), 3.20-3.31 (1H, m), 3.22 (1H, dd, J=13.5 and 9.2Hz), 3.81-3.92 (1H, m), 4.16-4.28 (1H, m), 4.67 (1H, J=5.8Hz), 5.10-5.22 (1H, m), 5.84 (1H, s), 7.14 (1H, d, J=10.3Hz), 7.15-7.32 (5H, m), 7.43 (1H, d, J=10.2Hz), 9.77 (1H, br. s);
MASS (ES+): m/e 513.26 (M+1).

Preparation C12

Preparation C12-1

Compound C12-1 was obtained in a manner similar to Preparation C1-1.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.04 (3x3H, s), 1.26-1.40 (4H, m), 1.33 (3H, d, J=7Hz), 1.48-1.92 (6H, m), 2.16 (1H, m), 2.34 (1H, m), 2.54 (2H, m), 2.90 (1H, dd, J=13 and 5Hz), 3.02 (1H, m), 3.18 (1H, dd, J=13 and 10Hz), 3.90 (1H, m), 3.92 (1H, q, J=7Hz), 4.32 (1H, dt, J=10 and 7.5Hz), 4.49 (1H, d, J=12Hz), 4.55 (1H, d, J=12Hz), 4.59 (1H, m), 5.01 (1H, ddd, J=10, 10 and 5Hz), 6.21 (1H, d, J=10Hz), 6.23 (1H, d, J=10Hz), 7.13 (1H, d, J=10Hz), 7.16-7.41 (10H, m);
MASS (ES+): m/e 647.

Example 1

Example 1-1

(1) To a stirred solution of dimethyl (3R)-tert-butyldimethylsilyloxy-2-oxobutylphosphonate (812 mg) in water and tetrahydrofuran (1:40) (7.5 ml) was added barium hydroxide octahydrate (482 mg) in one portion. The mixture was stirred at ambient temperature for 30 minutes. To the mixture was added a solution of Compound C1-3 (980 mg) in water and tetrahydrofuran (1:40) (1.5 ml once, 1 ml twice), and stirred for 1 hour. 10% Aqueous citric acid solution (50 ml) was added to the mixture to quench the reaction, stirred for 15 minutes under ice-cooling, and extracted with ethyl acetate (300 ml). The organic layer was washed with 10% citric acid (50 ml), water (50 ml) and brine (50 ml), dried over sodium sulfate and evaporated in vacuo. The residue was purified by flash column chromatography (eluted with

ethyl acetate/hexane = 2:3 to 1:1 v/v) to give Compound E1-1(1) as a white foam (852 mg).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, s), 1.09 (9H, s), 1.22 (3H, d, J=7.0Hz), 1.28 (3H, s), 1.37-1.51 (2H, m), 1.54-1.89 (4H, m), 2.09-2.37 (6H, m), 2.89 (1H, dd, J=14.0 and 6.2Hz), 3.18 (1H, dd, J=14.0 and 9.9Hz), 3.19-3.29 (1H, m), 3.80-3.91 (1H, m), 4.15-4.28 (1H, m), 4.27 (1H, q, J=7.0Hz), 4.63-4.70 (1H, m), 5.02 (2H, s), 5.06-5.19 (1H, m), 5.84 (1H, s), 6.61 (1H, d, J=15.4Hz), 6.80-6.89 (1H, m), 6.88 (2H, d, J=8.5Hz), 7.10-7.15 (1H, m), 7.14 (2H, d, J=8.5Hz), 7.28-7.49 (11H, m), 7.51 (1H, d, J=10.7Hz), 7.55-7.69 (4H, m);

MASS (ES+): m/e 885.56 (M+).

(2) Compound E1-1(2) was obtained in a manner similar to Example 1-1(1).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=6.7Hz), 1.09 (9H, s), 1.23 (3H, d, J=6.5Hz), 1.28 (3H, s), 1.35-1.53 (2H, m), 1.62-1.90 (3H, m), 2.09-2.38 (7H, m), 2.89 (1H, dd, J=13.5 and 5.8Hz), 3.18 (1H, dd, J=13.5 and 9.9Hz), 3.21-3.31 (1H, m), 3.81-3.92 (1H, m), 4.15-4.27 (1H, m), 4.27 (1H, q, J=6.5Hz), 4.67 (1H, br. d, J=5.6Hz), 5.03 (2H, s), 5.08-5.19 (1H, m), 5.79 (1H, s), 6.61 (1H, d, J=15.8Hz), 6.81-6.92 (1H, m), 6.88 (2H, d, J=8.8Hz), 7.09-7.17 (1H, m), 7.14 (2H, d, J=8.8Hz), 7.30-7.46 (11H, m), 7.50 (1H, d, J=10.7Hz), 7.57-7.62 (2H, m), 7.63-7.69 (2H, m);

MASS (ES+): m/e 885.45 (M+).

Example 1-2

(1) To a solution of the Compound E1-1(1) (86.9 ml) in methanol (3 ml), Pd-$BaSO_4$ (56.2 mg) was added and stirred for 1.25 hours under hydrogen atmosphere. The catalyst was filtered through a pad of Celite® and the solvent was evapolated under reduced pressure. The residue was purified by preparative thin layer chromatography to give Compound E1-2(1) as an oil (74.7 mg).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.10 (9H, s), 1.26 (3H, d, J=6.6Hz), 1.10-1.36 (6H, m), 1.27 (3H, s), 1.40-1.65 (3H, m), 1.67-1.85 (4H, m), 2.08-2.27 (2H, m), 2.27-2.40 (2H, m), 2.49 (2H, ddd, J=9.2, 7.0 and 1.5Hz), 2.88 (1H, dd, J=13.8 and 5.9Hz), 3.18 (1H, dd, J=13.8 and 9.9Hz), 3.18-3.30 (1H, m), 3.81-3.92 (1H, m), 4.14-4.24 (2H, m), 4.18 (1H, d, J=5.8Hz), 5.02 (2H, s), 5.13 (1H, ddd, J=16.1, 9.9 and 6.2Hz), 5.84 (1H, s), 6.88 (2H, d, J=8.8Hz), 7.07 (1H, d, J=10.3Hz), 7.15 (2H, d, J=8.4Hz), 7.25-

7.45 (11H, m), 7.56 (1H, d, J=10.38Hz), 7.55-7.68 (4H, m).

(2) To a solution of the Compound E1-1(1) in methanol-dioxane mixture (1:1) (20 ml) was added 10% palladium on carbon (300 mg) and the mixture was shaken under an atmosphere of hydrogen (4 atm) at ambient temperature for 20 hours. The mixture was filtered through a pad of Celite® and the filtrate was purified by flash chromatography (eluted with ethyl acetate/hexane = 1:1 to 2:2 v/v) to give Compound E1-2(2) as a colorless amorphous compound (610 mg).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.10 (9H, s), 1.14-1.56 (6H, m), 1.19 (3H, d, J=6.8Hz), 1.28 (3H, s), 1.69-1.88 (4H, m), 2.07-2.24 (2H, m), 2.24-2.37 (2H, m), 2.45-2.56 (2H, m), 2.88 (1H, dd, J=13.5 and 6.3Hz), 3.16 (1H, dd, J=13.5 and 9.8Hz), 3.20-3.31 (1H, m), 3.77-3.89 (1H, m), 4.11-4.20 (1H, m), 4.18 (1H, q, J=6.8Hz), 4.67 (1H, br. d, J=6.8Hz), 5.06-5.18 (1H, m), 5.10 (1H, s), 5.89 (1H, s), 6.73 (2H, d, J=8.4Hz), 7.05-7.10 (1H, m), 7.09 (2H, d, J=8.4Hz), 7.32-7.48 (6H, m), 7.53-7.70 (5H, m);
MASS (ES+): m/e 797.55 (M+).

(3) Compound E1-2(3) was obtained from the Compound E1-1(2) in a manner similar to Example 1-2(2).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.10 (9H, s), 1.19 (3H, d, J=6.7Hz), 1.21-1.61 (7H, m), 1.28 (3H, s), 1.69-1.88 (3H, m), 2.08-2.24 (2H, m), 2.25-2.38 (2H, m), 2.51 (2H, t, J=6.8Hz), 2.89 (1H, dd, J=13.5 and 6.2Hz), 3.16 (1H, dd, J=13.5 and 9.6Hz), 3.21-3.31 (1H, m), 3.77-3.90 (1H, m), 4.08-4.24 (2H, m), 4.67 (1H, br. d, J=5.9Hz), 5.05-5.18 (1H, m), 5.20 (1H, s), 5.85 (1H, s), 7.04-7.10 (1H, m), 7.09 (2H, d, J=8.5Hz), 7.32-7.48 (6H, m), 7.53-7.68 (5H, m);
MASS (ES+): m/e 797.57 (M).

Example 1-3

(1) To a stirred solution of the Compound E1-2(1) (74.7 mg) in tetrahydrofuran (3 ml) was added tetrabutylammonium fluoride (1.0M in tetrahydrofuran, 0.1 ml) at ambient temperature and the mixture was stirred for 40 minutes at the same temperature. The reaction mixture was diluted with water (10 ml) and the organic layer was extracted with ethyl acetate (5 ml, twice). The combined organic phase was washed with brine (5 ml), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified

by preparative thin layer chromatography (chloroform : methanol = 10:1 v/v) to give Compound E1-3(1) (51.6 mg) as a colorless oil.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.20-1.40 (4H, m), 1.28 (3H, s), 1.37 (3H, d, J=7.0Hz), 1.56-1.70 (2H, m), 1.70-1.88 (2H, m), 2.08-2.24 (2H, m), 2.25-2.58 (4H, m), 2.89 (1H, dd, J=13.6 and 5.9Hz), 3.18 (1H, dd, J=13.6 and 9.9Hz), 3.19-3.30 (1H, m), 3.61 (1H, d, J=4.4Hz), 3.80-3.90 (1H, m), 4.15-4.28 (2H, m), 4.68 (6.6H, d), 5.02 (2H, s), 5.15 (1H, ddd, J=16.1, 9.9 and 6.2Hz), 5.89 (1H, s), 6.88 (2H, d, J=8.8Hz), 7.10-7.18 (3H, m), 7.25-7.45 (5H, m), 7.54 (1H, d, J=10.3Hz);
MASS(ES+): m/e 648.35 (M+1).

(2) Compound E1-3(2) was obtained from the Compound E1-2(3) in a manner similar to Example 1-3(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=6.9Hz), 1.22-1.69 (7H, m), 1.28 (3H, s), 1.38 (3H, d, J=7.1Hz), 1.70-1.88 (3H, m), 2.07-2.24 (2H, m), 2.24-2.36 (2H, m), 2.88 (1H, dd, J=13.4 and 5.5Hz), 3.15 (1H, dd, J=13.4 and 9.4Hz), 3.20-3.32 (1H, m), 3.57 (1H, d, J=4.6Hz), 3.77-3.89 (1H, m), 4.13-4.28 (2H, m), 4.68 (1H, br. d, J=5.8Hz), 5.05-5.18 (1H, m), 5.40 (1H, s), 5.89 (1H, s), 6.73 (2H, d, J=8.0Hz), 7.09 (2H, d, J=8.0Hz), 7.12 (1H, d, J=10.0Hz), 7.55 (1H, d, J=10.2Hz);
MASS (ES+): m/e 559.41 (M+1).

(3) Compound E1-3(3) was obtained from the Compound E1-2(2) in a manner similar to Example 1-3(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.1Hz), 1.21-1.41 (4H, m), 1.29 (3H, s), 1.38 (3H, d, J=7.0Hz), 1.53-1.69 (3H, m), 1.70-1.89 (3H, m), 2.06-2.23 (2H, m), 2.24-2.38 (2H, m), 2.39-2.55 (2H, m), 2.88 (1H, dd, J=13.5 and 5.8Hz), 3.15 (1H, dd, J=13.5 and 9.6Hz), 3.19-3.31 (1H, m), 3.57 (1H, d, J=4.7Hz), 3.77-3.89 (1H, m), 4.07-4.29 (2H, m), 4.67 (1H, br d, J=6.5Hz), 5.06-5.18 (1H, m), 5.29 (1H, s), 15.93 (1H, s), 6.73 (2H, d, J=8.5Hz), 7.09 (2H, d, J=8.5Hz), 7.12 (1H, d, J=10.0Hz), 7.55 (1H, d, J=10.3Hz);
MASS (ES+): m/e 559.31 (M+1).

Example 2

Example 2-1

(1) Compound E2-1(1) was obtained from the Compound C2-3 in a manner similar to Example 1-1(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.3Hz), 1.09 (3x3H, s), 1.22 (3H, d, J=7Hz), 1.28 (3H, s), 1.38-1.52 (2H, m), 1.56-1.90

(4H, m), 2.08-2.40 (6H, m), 2.89 (1H, dd, J=14 and 6Hz), 3.18 (1H, dd, J=14 and 10Hz), 3.26 (1H, m), 3.77 (3H, s), 3.86 (1H, m), 4.21 (1H, m), 4.26 (1H, q, J=7Hz), 4.66 (1H, m), 5.14 (1H, ddd, J=10, 10 and 6Hz), 5.84 (1H, s), 6.62 (1H, br-d, J=16Hz), 6.81 (2x1H, d, J=8.5Hz), 6.84 (1H, dt, J=16 and 7Hz), 7.14 (2x1H, d, J=8.5Hz), 7.29-7.45 (6H, m), 7.51 (1H, d, J=10Hz), 7.55-7.68 (4H, m);

MASS (ES-): m/e 807.

(2) Compound E2-1(2) was obtained from the Compound C2-3 in a manner similar to Example 1-1(2).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.8Hz), 1.21 (9H, s), 1.26 (3H, d, J=6.9Hz), 1.63 (3H, s), 1.70-1.58 (4H, m), 1.71-1.79 (3H, m), 2.09-2.39 (6H, m), 2.89 (1H, dd, J=13.8 and 5.7Hz), 3.18 (1H, dd, J=13.8 and 9.6Hz), 3.22-3.31 (1H, m), 3.77 (3H, s), 3.79-3.92 (1H, m), 4.18-4.27 (1H, m), 4.27 (1H, q, J=6.9Hz), 5.13 (1H, ddd, J=9.9, 9.9 and 5.7Hz), 5.84 (1H, s), 6.61 (1H, d, J=15.3Hz), 6.81 (2H, d, J=8.7Hz), 6.86 (1H, dt, J=15.3 and 6.9Hz), 7.15 (2H, d, J=8.7Hz), 7.31-7.48 (5H, m), 7.51 (1H, d, J=10.5Hz), 7.57-7.69 (5H, m);

MASS (ES+): m/e 809.48 (M).

Example 2-2

(1) Compound E2-2(1) was obtained from the Compound E2-1(1) in a manner similar to Example 1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.3Hz), 1.10 (3x3H, s), 1.18 (3H, d, J=7Hz), 1.20-1.30 (4H, m), 1.28 (3H, s), 1.40-1.51 (2H, m), 1.60 (1H, m), 1.68-1.88 (3H, m), 2.09-2.24 (2H, m), 2.25-2.38 (2H, m), 2.51 (2H, m), 2.89 (1H, dd, J=13.5 and 6Hz), 3.18 (1H, dd, J=13.5 and 10Hz), 3.26 (1H, m), 3.85 (1H, m), 4.18 (1H, m), 4.18 (1H, q, J=7Hz), 4.67 (1H, m), 5.13 (1H, ddd, J=10, 10 and 6Hz), 5.85 (1H, s), 6.81 (2x1H, d, J=8.5Hz), 7.08 (1H, d, J=10Hz), 7.14 (2x1H, d, J=8.5Hz), 7.33-7.48 (6H, m), 7.56 (1H, d, J=10Hz), 7.59-7.68 (4H, m);

MASS (ES+): m/e 811.

(2) Compound E2-2(2) was obtained from the Compound E2-1(2) in a manner similar to Example 1-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.5Hz), 1.10 (9H, s), 1.16-1.32 (11H, m), 1.18 (3H, d, J=6.6Hz), 1.38-1.51 (1H, m), 1.61 (3H, s), 1.68-1.88 (2H, m), 2.08-2.24 (2H, m), 2.25-2.39 (2H, m), 2.50 (2H, t), 2.89 (1H, dd, J=13.5 and 6.0Hz), 3.18 (1H, dd,

J=13.5 and 9.9Hz), 3.23-3.30 (1H, m), 3.77 (3H, s), 3.81-3.90 (1H, m), 4.13-4.23 (1H, m), 4.18 (1H, q, J=6.6Hz), 4.64-4.69 (1H, m), 5.13 (1H, ddd, J=9.9, 9.9 and 6.3Hz), 5.84 (1H, s), 6.81 (2H, d, J=8.7Hz), 7.08 (1H, d, J=9.9Hz), 7.15 (2H, d, J=8.7Hz), 7.33-7.48 (6H, m), 7.55 (1H, d, J=10.2Hz);
MASS (ES+): m/e 811.49.

Example 2-3

(1) Compound E2-3(1) was obtained from the Compound E2-2(1) in a manner similar to Example 1-3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.3Hz), 1.20-1.40 (4H, m), 1.29 (3H, s), 1.38 (3H, d, J=7Hz), 1.54-1.69 (3H, m), 1.70-1.90 (3H, m), 2.08-2.23 (2H, m), 2.26-2.56 (4H, m), 2.89 (1H, dd, J=14 and 6Hz), 3.18 (1H, dd, J=14 and 10Hz), 3.26 (1H, m), 3.56 (1H, d, J=5Hz), 3.86 (1H, m), 4.14-4.30 (2H, m), 4.67 (1H, m), 5.13 (1H, ddd, J=10, 10 and 6Hz), 5.87 (1H, s), 6.81 (2x1H, d, J=9Hz), 7.12 (1H, d, J=11Hz), 7.14 (2x1H, d, J=9Hz), 7.53 (1H, d, J=10Hz);
MASS (ES-): m/e 571;
$[\alpha]_D^{25}$ = -116.5° (c=0.31, $CHCl_3$).

(2) Compound E2-3(2) was obtained from the Compound E2-2(2) in a manner similar to Example 1-3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=6.9Hz), 1.23-1.40 (2H, m), 1.38 (3H, d, J=7.2Hz), 1.55-1.90 (6H, m), 1.64 (3H, s), 2.05-2.58 (6H, m), 2.88 (1H, dd, J=13.5 and 6.0Hz), 3.18 (1H, dd, J=13.5 and 9.9Hz), 3.21-3.30 (1H, m), 3.55 (1H, d, J=4.8Hz), 3.78 (3H, s), 3.80-3.90 (1H, m), 4.16-4.28 (1H, m), 4.19 (1H, q, 7.2Hz), 4.64-4.70 (1H, m), 5.13 (1H, ddd, J=9.9, 9.9 and 6.0Hz), 5.89 (1H, s), 6.81 (2H, d, J=8.4Hz), 7.12 (1H, d, J=9.3Hz), 7.14 (2H, d, J=8.4Hz), 7.53 (1H, d, J=10.2Hz);
MASS (ES+): m/e 573.49 (M+1).

Example 3

Example 3-1

Compound E3-1 was obtained from the Compound C3-3 in a manner similar to Example 1-1(1).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.0Hz), 1.10 (9H s), 1.23 (3H, d, J=6.9Hz), 1.29 (3H, s), 1.36-1.55 (2H, m), 1.63-1.90 (4H, m), 2.07-2.39 (6H, m), 2.95 (1H, dd, J=13.9 and 7.4Hz), 3.21 (1H, dd, J=13.9 and 8.7Hz), 3.22-3.34 (1H, m), 3.80-3.91 (1H, m), 4.18-4.29 (1H, m), 4.28 (1H, q, J=6.9Hz), 4.68 (1H, br. d,

J=7.1Hz), 5.08-5.20 (1H, m), 5.83 (1H, s), 6.62 (1H, d, J=15.7Hz), 6.82-6.98 (1H, m), 6.97 (2H, t, J=8.7Hz), 7.09 (1H, d, J=10.6Hz), 7.20 (2H, dd, J=8.7 and 5.4Hz), 7.29-7.48 (6H, m), 7.55 (1H, d, J=10.6Hz), 7.56-7.69 (4H, m);

MASS (ES+): m/e 797.59 (M+1).

Example 3-2

Compound E3-2 was obtained from the Compound E3-1 in a manner similar to Example 1-2 except that 10% palladium on carbon was used instead of Pd-$BaSO_4$.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.10 (9H, s), 1.16-1.32 (3H, m), 1.18 (3H, d, J=6.7Hz), 1.28 (3H, s), 1.38-1.62 (4H, m), 1.72-1.88 (3H, m), 2.09-2.38 (4H, m), 2.46-2.55 (2H, m), 2.93 (1H, dd, J=13.2 and 7.1Hz), 3.20 (1H, dd, J=13.2 and 8.7Hz), 3.22-3.32 (1H, m), 3.79-3.89 (1H, m), 4.12-4.24 (1H, m), 4.19 (1H, q, J=6.7Hz), 4.67 (1H, br. d, J=5.4Hz), 5.08-5.19 (1H, m), 5.83 (1H, s), 6.96 (2H, t, J=8.6Hz), 7.04 (1H, d, J=10.2Hz), 7.19 (2H, dd, J=8.6 and 5.5Hz), 7.32-7.48 (6H, m), 7.54-7.67 (5H, m);

MASS (ES+): m/e 799.52 (M).

Example 3-3

Compound E3-3 was obtained from the Compound E3-2 in a manner similar to Example 1-3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.24-1.39 (6H, m), 1.28 (3H, s), 1.38 (3H, d, J=7.2Hz), 1.54-1.69 (1H, m), 1.71-1.89 (3H, m), 2.08-2.58 (6H, m), 2.93 (1H, dd, J=13.9 and 6.3Hz), 3.20 (1H, dd, J=13.9 and 9.6Hz), 3.21-3.32 (1H, m), 3.55 (1H, d, J=4.7Hz), 3.78-3.91 (1H, m), 4.14-4.29 (2H, m), 4.68 (1H, br. d, J=5.8Hz), 5.08-5.19 (1H, m), 5.87 (1H, s), 6.96 (2H, t, J=8.8Hz), 7.07 (1H, d, J=10.4Hz), 7.19 (2H, dd, J=8.8 and 5.5Hz), 7.56 (1H, d, J=10.7Hz);

MASS (ES+): m/e 561.46 (M+1).

Example 4

Example 4-1

Compound E4-1 was obtained from the Compound C4-3 in a manner similar to Example 1-1(1).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 1.09 (9H, s), 1.22 (1H, d, J=7.2Hz), 1.37-1.88 (15H, m), 2.12-2.38 (3H, m), 2.43-2.58 (2H, m), 2.95 (1H, dd, J=13.5 and 6.0Hz), 3.25 (1H, dd, J=13.5 and 10.2Hz), 3.28-3.13 (1H, m), 3.85-3.95 (1H, m), 4.22 (1H, dt, J=10.2 and 7.8Hz), 4.27 (1H, q, J=7.2Hz), 4.64-4.69 (1H, m), 5.15 (1H, ddd,

J=9.9, 9.9 and 5.7Hz), 6.16 (1H, s), 6.61 (1H, d, J=15.6Hz), 6.87 (1H, dt, J=15.6 and 6.9Hz), 7.16-7.33 (5H, m), 7.33-7.48 (8H, m), 7.57-7.74 (4H, m);
MASS (ES+): m/e 791.60 (M).

Example 4-2

Compound E4-2 was obtained from the Compound E4-1 in a manner similar to Example 1-2 except that 10% palladium on carbon was used instead of $Pd-BaSO_4$.
^1H-NMR (300MHz, $CDCl_3$, δ): 1.10 (9H, s), 1.01-1.84 (17H, m), 1.18 (3H, d, J=6.9Hz), 2.11-2.36 (2H, m), 2.41-2.58 (3H, m), 2.95 (1H, dd, J=10.5 and 6.0Hz), 3.15-3.26 (1H, m), 3.26 (1H, dd, J=10.5 and 13.5Hz), 3.84-3.94 (1H, m), 4.12 (1H, dt, J=6.9 and 7.5Hz), 4.18 (1H, q, J=6.9Hz), 4.63-4.69 (1H, m), 5.14 (1H, ddd, J=9.6, 9.6 and 6.0Hz), 6.14 (1H, s), 7.13 (1H, d, J=10.2Hz), 7.17-7.31 (4H, m), 7.32-7.49 (8H, m), 7.57-7.66 (4H, m);
MASS (ES+): m/e 793.57 (M).

Example 4-3

Compound E4-3 was obtained from the Compound E4-2 in a manner similar to Example 1-3.
^1H-NMR (300MHz, $CDCl_3$, δ): 1.19-1.87 (17H, m), 1.38 (3H, d, J=7.2Hz), 2.11-2.23 (1H, m), 2.24-2.39 (2H, m), 2.40-2.58 (2H, m), 2.95 (1H, dd, J=13.5 and 6.0Hz), 3.15-3.25 (1H, m), 3.25 (1H, dd, J=13.5 and 10.2Hz), 3.56 (1H, d, J=4.8Hz), 3.86-3.95 (1H, m), 4.12 (1H, q, J=7.2Hz), 4.28-4.12 (1H, m), 4.63-4.69 (1H, m), 5.15 (1H, ddd, J=10.2, 10.2 and 6.0Hz), 6.18 (1H, s), 7.14-7.34 (6H, m), 7.43 (1H, d, J=10.2Hz);
MASS (ES+): m/e 555.41 (M+1).

Example 5

Example 5-1

Compound E5-1 was obtained from the Compound C5-3 in a manner similar to Example 1-1(1).
^1H-NMR (300MHz, $CDCl_3$, δ): 0.812 (3H, t, J=7.2Hz), 1.10 (6H, s), 1.11 (3H, s), 1.27 (3H, s), 1.37-1.91 (8H, m), 2.08-2.39 (6H, m), 3.06 (1H, dd, J=14.7 and 6.9Hz), 3.25-3.36 (1H, m), 3.27 (1H, dd, J=14.7 and 8.7Hz), 3.80-3.89 (1H, m), 4.18-4.31 (1H, m), 4.26 (2H, t, J=6.6Hz), 4.66-4.71 (1H, m), 5.13-5.23 (1H, m), 5.89 (1H, s), 6.62 (1H, d, J=15.9Hz), 6.87 (1H, dt, J=15.9 and 6.9Hz), 7.01 (1H, d, J=10.8Hz), 7.30-7.49 (7H, m), 7.56-7.68 (8H, m);
MASS (ES+): m/e 804.62 (M+1).

Example 5-2

Compound E5-2 was obtained from the Compound E5-1 in a manner similar to Example 1-2 except that 10% palladium on carbon was used instead of 5% Pd-$BaSO_4$.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.807 (3H, t, J=6.9Hz), 1.10 (9H, s), 1.28 (3H, s), 1.38-1.90 (11H, m), 2.06-2.39 (6H, m), 2.51 (2H, dt, J=7.2 and 2.7Hz), 3.06 (1H, dd, J=13.5 and 7.5Hz), 3.26-3.36 (1H, m), 3.27 (1H, dd, J=13.5 and 9.0Hz), 3.79-3.88 (1H, m), 4.19 (1H, dq, J=6.6 and 2.7Hz), 4.25 (1H, dt, J=13.8 and 6.9Hz), 4.66-4.71 (1H, m), 5.18 (1H, dt, J=9.6 and 8.1Hz), 5.87 (1H, s), 6.95 (1H, d, J=10.2Hz), 7.32-7.49 (7H, m), 7.58-7.69 (7H, m), 7.58 (1H, d, J=9.0Hz);
MASS (ES+): m/e 806.38 (M+1).

Example 5-3

Compound E5-3 was obtained from the Compound E5-2 in a manner similar to Example 1-3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.811 (3H, t, J=7.5Hz), 1.24-1.68 (11H, m), 1.38 (3H, d, J=7.2Hz), 1.75-1.89 (3H, m), 2.06-2.57 (6H, m), 3.06 (1H, dd, J=14.1 and 7.5Hz), 3.26-3.36 (1H, m), 3.26 (1H, dd, J=14.1 and 8.7Hz), 3.79-3.88 (1H, m), 4.15-4.28 (2H, m), 4.65-4.71 (1H, m), 5.18 (1H, dt, J=8.4 and 7.2Hz), 5.90 (1H, s), 6.99 (1H, d, J=10.5Hz), 7.33-7.39 (2H, m), 7.56-7.61 (2H, m), 7.63 (1H, d, J=10.2Hz);
MASS (ES+): m/e 568.50 (M+1).

Example 6

Example 6-1

Compound E6-1 was obtained from the Compound C6-3 in a manner similar to Example 1-1.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=7.2Hz), 1.09 (5H, s), 1.10 (4H, s), 1.22 (3H, d, J=6.9Hz), 1.28 (3H, s), 1.37-1.90 (8H, m), 1.39 (3H, t, J=6.9Hz), 2.10-2.38 (4H, m), 2.88 (1H, dd, J=13.5 and 5.7Hz), 3.19 (1H, dd, J=13.5 and 9.6Hz), 3.12-3.30 (1H, m), 3.81-3.90 (1H, m), 3.99 (2H, q, J=6.9Hz), 4.16-4.31 (2H, m), 4.64-4.69 (1H, m), 5.13 (1H, dt, J=9.6 and 5.7Hz), 5.85 (1H, s), 6.61 (1H, d, J=15.9Hz), 6.79 (2H, d, J=8.4Hz), 6.86 (1H, dt, J=15.9Hz), 7.12-7.17 (1H, m), 7.13 (2H, d, J=8.4Hz), 7.31-7.47 (5H, m), 7.50 (1H, d, J=10.2Hz), 7.56-7.68 (5H, m);
MASS (ES+): m/e 823.64 (M+1).

Example 6-2

Compound E6-2 was obtained from the Compound E6-1 in a manner similar to Example 3-2.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.85 (3H, t, J=7.2Hz), 1.11 (9H, s), 1.20 (3H, d, J=6.9Hz), 1.20-1.65 (7H, m), 1.29 (3H, s), 1.40 (3H, t, J=6.9Hz), 1.71-1.86 (3H, m), 2.09-2.24 (2H, m), 2.26-2.38 (2H, m), 2.52 (1H, dt, J=7.5 and 2.1Hz), 2.89 (1H, dd, J=13.5 and 5.7Hz), 3.13-3.31 (1H, m), 3.23 (1H, dd, J=13.5 and 9.6Hz), 3.81-3.90 (1H, m), 4.00 (1H, q, J=6.9Hz), 4.19 (1H, dq, J=6.9 and 2.1Hz), 4.64-4.70 (1H, m), 5.14 (1H, dt, J=9.6 and 5.7Hz), 5.83 (1H, s), 6.80 (2H, d, J=8.7Hz), 7.10 (1H, d, J=11.1Hz), 7.14 (2H, d, J=8.7Hz), 7.34-7.48 (5H, m), 7.55 (1H, d, J=10.5Hz), 7.60-7.67 (5H, m);
MASS (ES+): m/e 825.65 (M+1).

Example 6-3

Compound E6-3 was obtained from the Compound E6-2 in a manner similar to Example 1-3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.84 (3H, t, J=6.9Hz), 1.20-1.42 (7H, m), 1.28 (3H, s), 1.39 (3H, t, J=7.2Hz), 1.52-1.69 (3H, m), 1.71-1.87 (3H, m), 2.08-2.24 (2H, m), 2.26-2.39 (2H, m), 2.46 (2H, dt, J=11.7 and 7.2Hz), 2.88 (1H, dd, J=13.2 and 5.7Hz), 3.17 (1H, dd, J=13.2 and 11.2Hz), 3.22-3.30 (1H, m), 3.55 (1H, d, J=4.5Hz), 3.81-3.90 (1H, m), 3.99 (2H, q, J=7.2Hz), 4.14-4.28 (2H, m), 4.64-4.69 (1H, m), 5.13 (1H, dt, J=11.2 and 5.7Hz), 5.84 (1H, s), 7.08-7.16 (1H, m), 7.13 (2H, d, J=8.4Hz), 7.52 (1H, d, J=10.5Hz);
MASS (ES+): m/e 587.56 (M+1).

Example 7

Example 7-1

(1) Compound E7-1(1) was obtained from the Compound C7-3 in a manner similar to Example 1-1(1).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.79 (3H, t, J=7Hz), 1.09 (3x3H, s), 1.22 (3H, d, J=7Hz), 1.26 (3H, s), 1.45 (2H, m), 1.65 (1H, m), 1.74-1.93 (3H, m), 2.10-2.40 (6H, m), 3.11 (1H, dd, J=15 and 8Hz), 3.15 (1H, dd, J=15 and 8Hz), 3.40 (1H, m), 3.88 (1H, m), 4.21 (1H, m), 4.27 (1H, q, J=7Hz), 4.69 (1H, m), 5.24 (1H, ddd, J=9, 8 and 8Hz), 5.80 (1H, s), 6.62 (1H, d, J=16Hz), 6.87 (1H, dt, J=16, 7Hz), 6.96-7.13 (3H, m), 7.15-7.27 (2H, m), 7.30-7.48 (6H, m), 7.52 (3H, d, J=9Hz), 7.55-7.70 (4H, m);
MASS (ES-): m/e 795.

(2) Compound E7-1(2) was obtained from the Compound C7-3 in

a manner similar to Example 1-1(2).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.78 (3H, t, J=7Hz), 1.09 (3x3H, s), 1.22 (3H, d, J=7Hz), 1.26 (3H, s), 1.45 (2H, m), 1.65 (1H, m), 1.72-1.92 (3H, m), 2.10-2.40 (6H, m), 3.11 (1H, dd, J=15 and 8Hz), 3.15 (1H, dd, J=15 and 8Hz), 3.40 (1H, m), 3.88 (1H, m), 4.21 (1H, m), 4.27 (1H, q, J=7Hz), 4.70 (1H, dd, J=8 and 2Hz), 5.23 (1H, ddd, J=9, 8 and 8Hz), 5.78 (1H, s), 6.61 (1H, d, J=16Hz), 6.86 (1H, dt, J=16 and 7Hz), 6.96-7.12 (3H, m), 7.15-7.28 (2H, m), 7.30-7.48 (6H, m), 7.52 (1H, d, J=9Hz), 7.55-7.69 (4H, m);

MASS (ES-): m/e 795.

(3) Compound E7-1(3) was obtained from the Compound C7-3 in a manner similar to Example 1-1(1) except that dimethyl (3R)-tert-butyldimethylsilyloxy-2-oxopentylphosphonate was used instead of dimethyl (3R)-tert-butyldimethylsilyloxy-2-oxobutylphosphonate.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.79 (3H, t, J=7Hz), 0.80 (3H, t, J=7Hz), 1.10 (3x3H, s), 1.26 (3H, s), 1.42 (2H, m), 1.55-1.70 (3H, m), 1.72-1.91 (3H, m), 2.10-2.41 (6H, m), 3.11 (1H, dd, J=14 and 8Hz), 3.15 (1H, dd, J=14 and 8Hz), 3.41 (1H, m), 3.89 (1H, m), 4.14 (1H, q, J=7Hz), 4.21 (1H, m), 4.69 (1H, m), 5.24 (1H, ddd, J=10, 8 and 8Hz), 5.78 (1H, s), 6.55 (1H, d, J=16Hz), 6.80 (1H, dt, J=16 and 7Hz), 6.97-7.12 (3H, m), 7.15-7.27 (2H, m), 7.29-7.47 (6H, m), 7.52 (1H, d, J=10Hz), 7.55-7.67 (4H, m);

MASS (ES-): m/e 809.

Example 7-2

(1) Compound E7-2(1) was obtained from the Compound E7-1(1) in a manner similar to Example 1-2 except that 10% palladium on carbon was used instead of Pd-$BaSO_4$.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.79 (3H, t, J=7Hz), 1.10 (3x3H, s), 1.15-1.34 (4H, m), 1.18 (3H, d, J=7Hz), 1.45 (2H, m), 1.60 (1H, m), 1.72-1.92 (3H, m), 2.08-2.40 (4H, m), 2.50 (2H, m), 3.10 (1H, dd, J=15 and 8Hz), 3.15 (1H, dd, J=15 and 7.5Hz), 3.41 (1H, m), 3.87 (1H, m), 4.18 (1H, m), 4.18 (1H, q, J=7Hz), 4.69 (1H, m), 5.23 (1H, ddd, J=10, 8 and 7.5Hz), 5.80 (1H, s), 6.96-7.08 (3H, m), 7.15-7.27 (2H, m), 7.32-7.49 (6H, m), 7.55 (1H, d, J=10Hz), 7.55-7.70 (5H, m);

MASS (ES-): m/e 797.

(2) Compound E7-2(2) was obtained from the Compound E7-1(2) in a manner similar to Example 1-2 except that 10% palladium on

carbon was used instead of Pd-$BaSO_4$.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.79 (3H, t, J=7Hz), 1.10 (3x3H, s), 1.15-1.32 (4H, m), 1.18 (3H, d, J=7Hz), 1.45 (2H, m), 1.60 (1H, m), 1.71-1.92 (3H, m), 2.09-2.40 (4H, m), 2.51 (2H, t, J=7Hz), 3.10 (1H, dd, J=15 and 8Hz), 3.15 (1H, dd, J=15 and 8Hz), 3.40 (1H, m), 3.87 (1H, m), 4.18 (1H, q, J=7Hz), 4.18 (1H, m), 4.69 (1H, m), 5.23 (1H, ddd, J=10, 8 and 7.5Hz), 5.79 (1H, s), 6.95-7.09 (3H, m), 7.14-7.28 (2H, m), 7.32-7.49 (6H, m), 7.55 (1H, d, J=10Hz), 7.55-7.68 (6H, m);
MASS (ES-): m/e 797.

(3) Compound E7-2(3) was obtained from the Compound E7-1(3) in a manner similar to Example 1-2 except that 10% palladium on carbon was used instead of Pd-$BaSO_4$.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.79 (3H, t, J=7Hz), 0.81 (3H, t, J=7Hz), 1.11 (3x3H, s), 1.13-1.28 (4H, m), 1.26 (3H, s), 1.37 (2H, m), 1.49-1.67 (3H, m), 1.71-1.92 (3H, m), 2.08-2.49 (6H, m), 3.10 (1H, dd, J=15 and 8Hz), 3.15 (1H, dd, J=15 and 7.5Hz), 3.40 (1H, m), 3.87 (1H, m), 4.10 (1H, t, J=6Hz), 4.17 (1H, m), 4.69 (1H, m), 5.23 (1H, ddd, J=9, 8 and 7.5Hz), 5.79 (1H, s), 6.96-7.08 (3H, m), 7.14-7.28 (2H, m), 7.32-7.47 (6H, m), 7.55 (1H, d, J=9Hz), 7.55-7.66 (5H, m);
MASS (ES-): m/e 811.

Example 7-3

(1) Compound E7-3(1) was obtained from the Compound E7-2(1) in a manner similar to Example 1-3.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.80 (3H, t, J=7.5Hz), 1.24-1.42 (4H, m), 1.26 (3H, s), 1.38 (3H, d, J=7Hz), 1.54-1.70 (3H, m), 1.74-1.92 (3H, m), 2.08-2.58 (6H, m), 3.11 (1H, dd, J=15 and 8Hz), 3.15 (1H, dd, J=15 and 7Hz), 3.41 (1H, m), 3.58 (1H, d, J=5Hz), 3.87 (1H, m), 4.13-4.30 (2H, m), 4.70 (1H, m), 5.24 (1H, ddd, J=10, 8 and 7Hz), 5.84 (1H, s), 6.97-7.12 (3H, m), 7.15-7.30 (2H, m), 7.54 (1H, d, J=10Hz);
MASS (ES-): m/e 559;
MASS (ES+): m/e 561.

(2) Compound E7-3(2) was obtained from the Compound E7-2(2) in a manner similar to Example 1-3.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.80 (3H, t, J=7.5Hz), 1.20-1.42 (4H, m), 1.26 (3H, s), 1.38 (3H, d, J=7Hz), 1.53-1.73 (3H, m), 1.74-1.93 (3H, m), 2.09-2.59 (6H, m), 3.10 (1H, dd, J=15 and 8Hz),

3.15 (1H, dd, J=15 and 7Hz), 3.40 (1H, m), 3.56 (1H, d, J=5Hz), 3.87 (1H, m), 4.14-4.29 (2H, m), 4.70 (1H, m), 5.24 (1H, ddd, J=10, 8 and 7Hz), 5.83 (1H, s), 6.96-7.13 (3H, m), 7.15-7.29 (2H, m), 7.54 (1H, d, J=10Hz);
MASS (ES-): m/e 559.

(3) Compound E7-3(3) was obtained from the Compound E7-2(3) in a manner similar to Example 1-3.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.79 (3H, t, J=7.5Hz), 0.94 (3H, t, J=7.5Hz), 1.17-1.40 (4H, m), 1.26 (3H, s), 1.50-1.78 (4H, m), 1.79-1.97 (4H, m), 2.08-2.40 (6H, m), 2.45 (2H, m), 3.10 (1H, dd, J=15 and 7.5Hz), 3.14 (1H, dd, J=15 and 7.5Hz), 3.40 (1H, m), 3.51 (1H, d, J=5Hz), 3.87 (1H, m), 4.08-4.26 (2H, m), 4.70 (1H, m), 5.23 (1H, ddd, J=9, 7.5 and 7.5Hz), 5.85 (1H, s), 6.95-7.12 (3H, m), 7.14-7.31 (2H, m), 7.54 (1H, d, J=9Hz);
MASS (ES-): m/e 573;
MASS (ES+): m/e 575.

Example 8

Example 8-1

Compound E8-1 was obtained from the Compound C8-3 in a manner similar to Example 1-1(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.09 (3X3H, s), 1.22 (3H, d, J=7Hz), 1.28 (3H, s), 1.38-1.52 (2H, m), 1.64 (1H, m), 1.70-1.91 (3H, m), 2.08-2.38 (6H, m), 2.94 (1H, dd, J=14 and 6Hz), 3.20 (1H, dd, J=14 and 9.5Hz), 3.28 (1H, m), 3.86 (1H, m), 4.22 (1H, m), 4.27 (1H, q, J=7Hz), 4.67 (1H, m), 5.14 (1H ,ddd, J=10, 9.5 and 6Hz), 5.87 (1H, s), 6.62 (1H, d, J=16Hz), 6.86 (1H, dt, J=16.7Hz), 7.08 (1H, d, J=10Hz), 7.16 (2X1H, d, J=8.5Hz), 7.24 (2X1H, d, J=8.5Hz), 7.31-7.48 (6H, m), 7.52-7.69 (5H, m);
MASS (ES+): m/e 813.

Example 8-2

Compound E8-2 was obtained from the Compound E8-1 in a manner similar to Example 1-2.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7Hz), 1.10 (3X3H, s), 1.18 (3H, d, J=6.5Hz), 1.20-1.30 (4H, m), 1.28 (3H, s), 1.40-1.50 (2H, m), 1.60 (1H, m), 1.72-1.89 (3H, m), 2.08-2.38 (4H, m), 2.51 (2H, m), 2,94 (1H ,dd, J=14 and 6Hz), 3.20 (1H ,dd, J=14 and 10Hz), 3.28 (1H, m), 3.84 (1H, m), 4.19 (1H ,q, J=6.5Hz), 4.19 (1H, m), 4.67 (1H, m), 5.14 (1H, ddd, J=10, 10 and 6Hz), 5.87 (1H, s), 7.03 (1H, d, J=10.5Hz), 7.17 (2X1H, d, J=9Hz), 7.24 (2X1H, d,

J=9Hz), 7.33-7.50 (6H, m), 7,56-7.68 (5H, m);
MASS (ES+): m/e 815.

Example 8-3

Compound E8-3 was obtained from the Compound E8-2 in a manner similar to Example 1-3.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.20-1.40 (4H, m), 1.28 (3H ,s), 1.38 (3H ,d, J=7Hz), 1.55-1.70 (3H, m), 1.72-1.90 (3H, m), 2.08-2.58 (6H, m), 2.94 (1H, dd, J=14.6Hz), 3.20 (1H, dd, J=14 and 10Hz), 3.28 (1H, m), 3.56 (1H, d, J=5Hz), 3.85 (1H, m), 4.15-4.30 (2H, m), 4.68 (1H, m), 5.14 (1H, ddd, J=10, 10 and 6Hz), 5.90 (1H, s), 7.06 (1H, d, J=10Hz), 7.17 (2X1H, d, J=9Hz), 7.24 (2X1H, d, J=9Hz), 7,58 (1H, d, J=10Hz);
MASS (ES+): m/e 577;
$[\alpha]_D^{25}$ = -116.1° (c=0.31, $CHCl_3$).

Example 9

Example 9-1

Compound E9-1 was obtained from the Compound C9-3 in a manner similar to Example 1-1(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.77 (3H, t, J=7.7Hz), 0.91 (3H, t, J=7.3Hz), 1.09 (9H, s), 1.22 (3H, d, J=7.0Hz), 1.37-1.70 (4H, m), 1.71-1.92 (4H, m), 2.07-2.45 (6H, m), 2.97 (1H, dd, J=13.5 and 5.8Hz), 3.18-3.31 (2H, m), 3.83-3.95 (1H, m), 4.15-4.29 (1H, m), 4.27 (1H, q, J=6.9Hz), 4.66 (1H, br. d, J=6.9Hz), 5.12-5.24 (1H, m), 5.79 (1H, s), 6.61 (1H, d, J=15.6Hz), 6.86 (1H, dt, J=15.6 and 6.7Hz), 7.13 (1H, d, J=9.9Hz), 7.17-7.29 (5H, m), 7.30-7.45 (6H, m), 7.49 (1H, d, J=10.6Hz), 7.56-7.69 (4H, m);
MASS (ES+): m/e 793.32 (M+1).

Example 9-2

Compound E9-2 was obtained from the Compound E9-1 in a manner similar to Example 3-2.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.77 (3H, t, J=7.3Hz), 0.92 (3H, t, J=7.3Hz), 1.11 (9H, s), 1.15-1.35 (4H, m), 1.19 (3H, t, J=6.6Hz), 1.37-1.69 (5H, m), 1.70-1.91 (3H, m), 2.11-2.46 (4H, m), 2.52 (2H, dt, J=7.0 and 2.5Hz), 2.97 (1H, dd, J=13.5 and 6.3Hz), 3.18-3.31 (2H, m), 3.82-3.96 (1H, m), 4.16-4.26 (1H, m), 4.19 (1H, q, J=6.5Hz), 4.67 (1H, d, J=5.9Hz), 5.12-5.24 (1H, m), 5.79 (1H, s), 7.08 (1H, d, J=10.6Hz), 7.17-7.32 (5H, m), 7.33-7.49 (6H, m), 7.53 (1H, d, J=10.5Hz), 7.58-7.69 (4H, m);
MASS (ES+): m/e 795.09 (M+1).

Example 9-3

Compound E9-3 was obtained from the Compound E9-2 in a manner similar to Example 1-3.

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.77 (3H, t, J=6.9Hz), 0.91 (3H, t, J=7.3Hz), 1.21-1.41 (4H, m), 1.38 (3H, d, J=7.0Hz), 1.51-1.70 (4H, m), 1.70-1.92 (4H, m), 2.08-2.58 (6H, m), 2.96 (1H, dd, J=13.6 and 6.4Hz), 3.16-3.30 (2H, m), 3.56 (1H, d, J=4.6Hz), 3.82-3.94 (1H, m), 4.13-4.29 (2H, m), 4.67 (1H, br. d, J=6.2Hz), 5.11-5.24 (1H, m), 5.81 (1H, s), 7.11 (1H, d, J=10.3Hz), 7.16-7.34 (5H, m), 7.50 (1H, d, J=10.4Hz);

MASS (ES+): m/e 557.29 (M+1).

Example 10

Example 10-1

(1) Compound E10-1(1) was obtained from the Compound C10-3 in a manner similar to Example 1-1(1).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.5Hz), 1.09 (3x3H, s), 1.22 (3H, d, J=7Hz), 1.28 (3H, s), 1.45 (2H, m), 1.56-1.90 (4H, m), 2.07-2.40 (6H, m), 2.97 (1H, dd, J=13.5 and 6.5Hz), 3.24 (1H, dd, J=13.5 and 9Hz), 3.27 (1H, m), 3.87 (1H, m), 4.21 (1H, m), 4.27 (1H, q, J=7Hz), 4.64 (1H, m), 5.19 (1H, ddd, J=10, 9 and 6.5Hz), 5.81 (1H, s), 6.62 (1H, br-d, J=16Hz), 6.87 (1H, dt, J=16, 7Hz), 7.13 (1H, d, J=10Hz), 7.17-7.49 (11H, m), 7.53 (1H, d, J=10Hz), 7.56-7.76 (4H, m);

MASS (ES-): m/e 777.

(2) Compound E10-1(2) was obtained from the Compound C10-3 in a manner similar to Example 1-1(2).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.82 (3H, t, J=7.3Hz), 1.09 (3x3H, s), 1.23 (3H, d, J=7Hz), 1.28 (3H, s), 1.45 (2H, m), 1.58-1.92 (4H, m), 2.08-2.40 (6H, m), 2.97 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 9.5Hz), 3.27 (1H, m), 3.87 (1H, m), 4.21 (1H, dt, J=10 and 7.5Hz), 4.27 (1H, q, J=7Hz), 4.67 (1H, dd, J=8 and 2.5Hz), 5.19 (1H, ddd, J=10, 9.5 and 6Hz), 5.81 (1H, s), 6.61 (1H, br.d, J=16Hz), 6.87 (1H, dt, J=16 and 7Hz), 7.13 (1H, d, J=10.5Hz), 7.16-7.49 (11H, m), 7.53 (1H, d, J=10Hz), 7.56-7.69 (4H, m);

MASS (ES-): m/e 777.

(3) Compound E10-1(3) was obtained from the Compound C10-3 in a manner similar to Example 7-1(3).

^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.80 (3H, t, J=7.4Hz), 0.83 (3H, t,

J=7.4Hz), 1.10 (3x3H, s), 1.28 (3H, s), 1.44 (2H, m), 1.54-1.90 (6H, m), 2.08-2.40 (6H, m), 2.97 (1H, dd, J=14 and 6Hz), 3.24 (1H, dd, J=14 and 9.5Hz), 3.27 (1H, m), 3.87 (1H, m), 4.15 (1H, t, J=6Hz), 4.20 (1H, m), 4.67 (1H, m), 5.19 (1H, ddd, J=10, 9.5 and 6Hz), 5.78 (1H, s), 6.55 (1H, d, J=16Hz), 6.80 (1H, dt, J=16 and 7Hz), 7.12 (1H, d, J=10.5Hz), 7.16-7.47 (11H, m), 7.53 (1H, d, J=10Hz), 7.53-7.68 (4H, m);
MASS (ES-): m/e 791.

Example 10-2

(1) Compound E10-2(1) was obtained from the Compound E10-1(1) in a manner similar to Example 3-2.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.10 (3x3H, s), 1.18 (3H, d, J=7Hz), 1.20-1.33 (4H, m), 1.28 (3H, s), 1.45 (2H, m), 1.60 (1H, m), 1.71-1.90 (3H, m), 2.08-2.40 (4H, m), 2.51 (2H, m), 2.97 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 9Hz), 3.27 (1H, m), 3.86 (1H, m), 4.18 (1H, m), 4.18 (1H, q, J=7Hz), 4.67 (1H, m), 5.18 (1H, ddd, J=10, 9 and 6Hz), 5.81 (1H, s), 7.07 (1H, d, J=10.5Hz), 7.16-7.31 (5H, m), 7.33-7.48 (6H, m), 7.57 (1H, d, J=10Hz), 7.58-7.74 (4H, m);
MASS (ES-): m/e 779.

(2) Compound E10-2(2) was obtained from the Compound E10-1(2) in a manner similar to Example 3-2.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.10 (3x3H, s), 1.16-1.33 (4H, m), 1.18 (3H, d, J=7Hz), 1.28 (3H, s), 1.46 (2H, m), 1.58 (1H, m), 1.68-1.88 (3H, m), 2.07-2.40 (4H, m), 2.51 (2H, t, J=7Hz), 2.97 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 9.5Hz), 3.27 (1H, m), 3.86 (1H, m), 4.18 (1H, m), 4.18 (1H, q, J=7Hz), 4.67 (1H, dd, J=8 and 2.5Hz), 5.18 (1H, ddd, J=10, 9.5 and 6Hz), 5.82 (1H, s), 7.08 (1H, d J=10Hz), 7.16-7.32 (5H, m), 7.33-7.50 (6H, m), 7.58 (1H, d, J=10Hz), 7.58-7.70 (5H, m);
MASS (ES-): m/e 779.

(3) Compound E10-2(3) was obtained from the Compound E10-1(3) in a manner similar to Example 3-2.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.81 (3H, t, J=7Hz), 0.83 (3H, t, J=7Hz), 1.11 (9H, s), 1.15-1.26 (4H, m), 1.28 (3H, s), 1.30-1.46 (2H, m), 1.50-1.85 (6H, m), 2.07-2.48 (6H, m), 2.97 (1H, dd, J=14 and 6Hz), 3.24 (1H, dd, J=14 and 9Hz), 3.26 (1H, m), 3.86 (1H, m), 4.10-4.23 (2H, m), 4.67 (1H, m), 5.19 (1H, m), 5.80 (1H, s), 7.06 (1H, d, J=10.5Hz), 7.16-7.31 (5H, m), 7.32-7.47 (6H, m), 7.54-

7.66 (5H, m);
MASS: (ES+) m/e 795.

Example 10-3

(1) Compound E10-3(1) was obtained from the Compound E10-1(3) in a manner similar to Example 1-3(1) except that pyridine hydrofluoride was used instead of tetrabutylammonium fluoride.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7Hz), 0.94 (3H, t, J=7Hz), 1.20-1.97 (8H, m), 1.29 (3H, s), 2.08-2.40 (6H, m), 2.97 (1H, dd, J=14 and 6Hz), 3.23 (1H, dd, J=14 and 9Hz), 3.26 (1H, m), 3.59 (1H, d, J=5Hz), 3.87 (1H, m), 4.22 (1H, m), 4.67 (1H, m), 5.19 (1H, ddd, J=10, 9 and 6Hz), 5.84 (1H, s), 6.26 (1H, d, J=16Hz), 7.00 (1H, dt, J=16 and 7Hz), 7.16 (1H, d, J=10Hz), 7.19-7.32 (5H, m), 7.50 (1H, d, J=10Hz);
MASS: (ES-) m/e 553.

(2) Compound E10-3(2) was obtained from the Compound E10-2(3) in a manner similar to Example 10-3(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7Hz), 0.94 (3H, t, J=7Hz), 1.22-1.40 (4H, m), 1.28 (3H, s), 1.52-1.70 (4H, m), 1.71-1.98 (4H, m), 2.08-2.24 (2H, m), 2.25-2.40 (2H, m), 2.45 (2H, m), 2.96 (1H, ddd, J=13, 6 and 5Hz), 3.18-3.32 (2H, m), 3.50 (1H, d, J=5Hz), 3.86 (1H, m), 4.14 (1H, m), 4.20 (1H, m), 4.67 (1H, m), 5.19 (1H, ddd, J=10, 9 and 6Hz), 5.82 (1H, s), 7.10 (1H, d, J=10Hz), 7.16-7.32 (5H, m), 7.54 (1H, d, J=10Hz);
MASS (ES+): m/e 557.

(3) Compound E10-3(3) was obtained from the Compound E10-1(1) in a manner similar to Example 10-3(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.29 (3H, s), 1.38 (3H, d, J=7Hz), 1.42-1.93 (6H, m), 2.07-2.40 (6H, m), 2.97 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 9.5Hz), 3.26 (1H, m), 3.65 (1H, d, J=5Hz), 3.87 (1H, m), 4.22 (1H, dt, J=10.5 and 7.5Hz), 4.44 (1H, dq, J=7 and 5Hz), 4.67 (1H, dd, J=8 and 2.5Hz), 5.19 (1H, ddd, J=10, 9.5 and 6Hz), 5.84 (1H, s), 6.24 (1H, br-d, J=16Hz), 7.01 (1H, dt, J=16 and 7Hz), 7.16 (1H, d, J=10.5Hz), 7.16-7.32 (5H, m), 7.50 (1H, d, J=10Hz);
MASS (ES-): m/e 539.

(4) Compound E10-3(4) was obtained from the Compound E10-2(1) in a manner similar to Example 10-3(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.20-1.42 (4H, m), 1.28 (3H, s), 1.38 (3H, d, J=7Hz), 1.54-1.90 (6H, m), 2.08-

2.58 (6H, m), 2.96 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 9Hz), 3.27 (1H, m), 3.57 (1H, d, J=4.5Hz), 3.86 (1H, m), 4.14-4.29 (2H, m), 4.67 (1H, dd, J=8 and 2.5Hz), 5.19 (1H, ddd, J=10, 9 and 6Hz), 5.82 (1H, s), 7.10 (1H, d, J=10Hz), 7.16-7.33 (5H, m), 7.55 (1H, d, J=10Hz), 3.57 (1H, d, J=4.5Hz);
MASS (ES-): m/e 541.

(5) Compound E10-3(5) was obtained from the Compound E10-2(2) in a manner similar to Example 10-3(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.5Hz), 1.20-1.41 (4H, m), 1.28 (3H, s), 1.38 (3H, d, J=7Hz), 1.52-1.90 (6H, m), 2.08-2.58 (6H, m), 2.96 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 9.5Hz), 3.27 (1H, m), 3.57 (1H, d, J=5Hz), 3.86 (1H, m), 4.14-4.29 (2H, m), 4.67 (1H, dd, J=8 and 2.5Hz), 5.18 (1H, ddd, J=10, 9.5 and 6Hz), 5.83 (1H, s), 7.10 (1H, d, J=10Hz), 7.16-7.31 (5H, m), 7.55 (1H, d, J=10Hz);
MASS (ES-): m/e 541.

Example 10-4

(1) To a solution of compound E10-3(5) (7.7 mg) in pyridine (0.8 ml) was added (R)-(-)-α-methoxy-α-trifluoromethyl-α-phenylacetyl chloride (7.7 mg) at 0°C and the mixture was stirred at ambient temperature until the Compound E10-3(5) was disappeared. The solvent was evaporated and the residue was purified by preparative thin layer chromatography (hexane/ethyl acetate = 1:3 v/v) to give Compound E10-4(1) as an oil (8.4 mg).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.20-1.38 (4H, m), 1.28 (3H, s), 1.44 (3H, d, J=7Hz), 1.54-1.90 (6H, m), 2.08-2.59 (6H, m), 2.97 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 9.5Hz), 3.28 (1H, m), 3.63 (3H, s), 3.88 (1H, m), 4.14-4.25 (2H, m), 4.67 (1H, dd, J=8.5 and 3Hz), 5.19 (1H, ddd, J=10, 9.5 and 6Hz), 5.24 (1H, q, J=7Hz), 5.81 (1H, s), 7.09 (1H, d, J=10Hz), 7.16-7.32 (5H, m), 7.40-7.48 (3H, m), 7.56 (1H, d, J=10Hz), 7.59-7.66 (2H, m);
MASS: (ES-) m/e 757.

(2) Compound E10-4(2) was obtained from the Compound E10-3(5) in a manner similar to Example 10-4(1) except that (S)-(-)-α-methoxy-α-trifluoromethyl-α-phenylacetyl chloride was used instead of (R)-(-)-α-methoxy-α-trifluoromethyl-α-phenylacetyl chloride.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.3Hz), 1.18-1.38 (4H,

m), 1,28 (3H, s), 1,46-1.87 (6H, m), 1.49 (3H, d, J=7Hz), 2.09-2.48 (6H, m), 2.96 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 9.5Hz), 3.27 (1H, m), 3.58 (3H ,s), 3.86 (1H, m), 4.12-4.26 (2H, m), 4.67 (1H, dd, J=8.2Hz), 5.18 (1H, m), 5.28 (1H, q, J=7Hz), 5.81 (1H, s), 7.08 (1H, d, J=10.5Hz), 7.16-7.32 (5H, m), 7.40-7.47 (3H, m), 7.51-7.62 (3H, m);
MASS (ES-): m/e 757.

(3) Compound E10-4(3) was obtained from the Compound 10-3(4) in a manner similar to Example 10-2(1).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.5Hz), 1.17-1.34 (4H, m), 1.28 (3H, s), 1.49 (3H, d, J=7Hz), 1.51-1.63 (3H, m), 1.70-1.88 (3H, m), 2.08-2.50 (6H, m), 2.96 (1H, dd, J=13.5 and 6.5Hz), 3.23 (1H, dd, J=13.5 and 9.5Hz), 3.27 (1H, m), 3.58 (3H, s), 3.86 (1H, m), 4.18 (1H, m), 4.67 (1H, m), 5.18 (1H, m), 5.29 (1H, q, J=7Hz), 5.80 (1H, s), 7.08 (1H, d, J=10Hz), 7.16-7.32 (5H, m), 7.40-7.47 (3H, m), 7.51-7.64 (3H, m);
MASS (ES-): m/e 757.

(4) Compound E10-4(4) was obtained from the Compound 10-3(4) in a manner similar to Example 10-2(2).
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.83 (3H, t, J=7.4Hz), 1.17-1.37 (4H, m), 1.28 (3H, s), 1.44 (3H, d, J=7Hz), 1.52-1.68 (3H, m), 1.70-1.90 (3H, m), 2.08-2.59 (6H, m), 2.97 (1H, dd, J=13.5 and 6Hz), 3.24 (1H, dd, J=13.5 and 10Hz), 3.27 (1H, m), 3.63 (3H, s), 3.86 (1H, m), 4.19 (1H, dt, J=10 and 7.5Hz), 4.67 (1H, dd, J=8 and 2Hz), 5.18 (1H, ddd, J=10, 10 and 6Hz), 5.25 (1H, q, J=7Hz), 5.81 (1H, s), 7.09 (1H, d, J=10Hz), 7.16-7.32 (5H, m), 7.40-7.48 (3H, m), 7.52-7.66 (2H, m), 7.56 (1H, d, J=10Hz);
MASS (ES-): m/e 757.

Example 11

Example 11-1

Compound E11-1 was obtained in a manner similar to Example 1-1.

Example 11-2

Compound E11-2 was obtained from the Compound E11-1 in a manner similar to Example 3-2.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.89 (3H, t, J=6.9Hz), 0.97 (3H, t, J=7.0Hz), 1.11 (9H, s), 1.16-1.67 (12H, m), 1.19 (3H, d, J=7.0Hz), 1.68-1.88 (4H, m), 2.00-2.45 (4H, m), 2.51 (2H, br. t, J=6.9Hz), 2.98 (1H, dd, J=13.1 and 6.3Hz), 3.21-3.32 (1H, m), 3.23 (1H, dd,

J=13.1 and 9.2Hz), 3.81-3.92 (1H, m), 4.13 (1H, q, J=7.1Hz), 4.15-4.23 (1H, m), 4.68 (1H, br. d, J=5.7Hz), 5.10-5.22 (1H, m), 5.80 (1H, s), 7.07 (1H, d, J=10.3Hz), 7.16-7.31 (6H, m), 7.33-7.48 (5H, m), 7.52 (1H, d, J=10.2Hz), 7.58-7.75 (4H, m);
MASS (ES+): m/e 823.31 (M+1).

Example 11-3

Compound E11-3 was obtained from the Compound E11-2 in a manner similar to Example 1-3.
^{1}H-NMR (300MHz, $CDCl_3$, δ): 0.89 (3H, t, J=6.5Hz), 0.96 (3H, t, J=6.9Hz), 1.12-1.41 (7H, m), 1.38 (3H, d, J=7.4Hz), 1.41-1.69 (5H, m), 1.70-1.88 (4H, m), 2.00-2.58 (6H, m), 2.98 (1H, dd, J=12.5 and 6.2Hz), 3.19-3.31 (1H, m), 4.12-4.29 (1H, dd, J=12.5 and 9.0Hz), 3.55 (1H, d, J=4.8Hz), 3.80-3.93 (1H, m), 4.12-4.29 (2H, m), 4.67 (1H, br.d, J=5.4Hz), 5.10-5.22 (1H, m), 5.81 (1H, s), 7.10 (1H, d, J=9.9Hz), 7.16-7.32 (5H, m), 7.49 (1H, d, J=10.5Hz);
MASS (ES+): m/e 585.34 (M+1).

Example 12

Examples 12-2

Compound E12-2 was obtained in a manner similar to Example 1-2.

Example 12-3

A solution of the Compound E12-2 (88 mg) in methanol (3 ml) was hydrogenated in the presence of palladium hydroxide, 20 wt% Pd (dry basis) on carbon (Pearlman's catalyst) (30 mg) for 2 hours. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was purified by preparative thin layer chromatography (eluted with chloroform : methanol = 20:1 v/v) to give Compound E12-3 as an amorphous (76 mg).
^{1}H-NMR (300MHZ, $CDCl_3$, δ): 1.04 (3x3H, s), 1.22-1.43 (4H, m), 1.38 (3H, d, J=7Hz), 1.56-1.93 (6H, m), 2.17 (1H, m), 2.26-2.58 (3H, m), 2.91 (1H, dd, J=13 and 5Hz), 3.02 (1H, m), 3.19 (1H, dd, J=13 and 11Hz), 3.57 (1H, d, J=5Hz), 3.91 (1H, m), 4.13 (1H, d, J=10.5Hz), 4.24 (1H, dq, J=7 and 5Hz), 4.33 (1H, dt, J=10 and 7.5Hz), 4.60 (1H, m), 5.02 (1H, ddd, J=11, 10 and 5Hz), 6.23 (1H, d, J=10.5Hz), 6.25 (1H, d, J=10Hz), 7.12-7.32 (6H, m);
MASS: (ES+): m/e 557.

The compounds used in the above-mentioned Preparations and Examples are listed in the following Table 2.

Table 2

Table 2-1

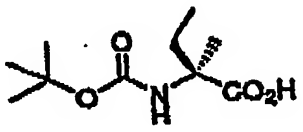
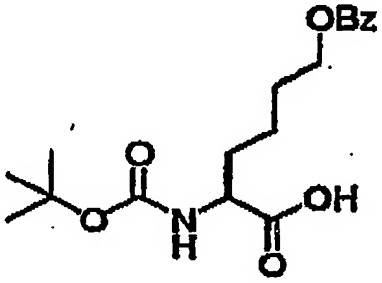
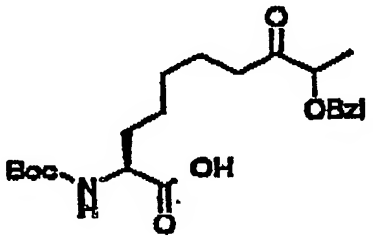
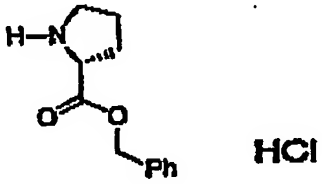
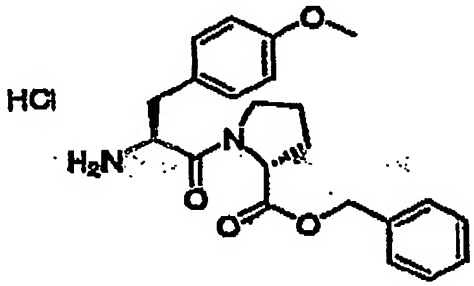
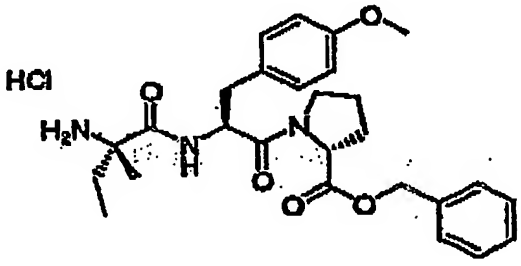
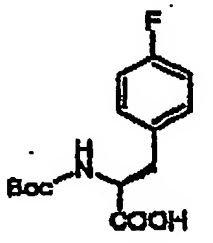
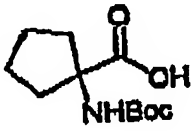
Compound a	Compound b
	
Compound c	**Compound d**
	
Compound e	**Compound f**
	
Compound g	**Compound h**
	

Table 2-2

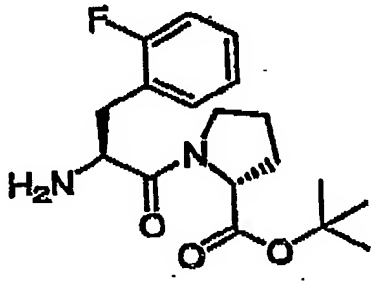
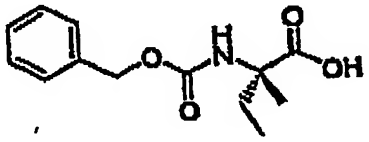
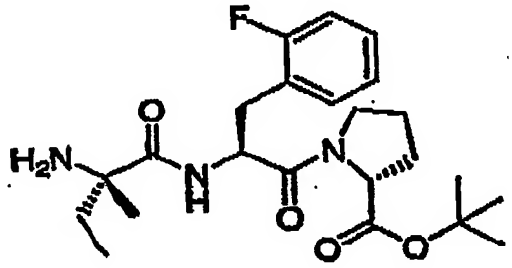
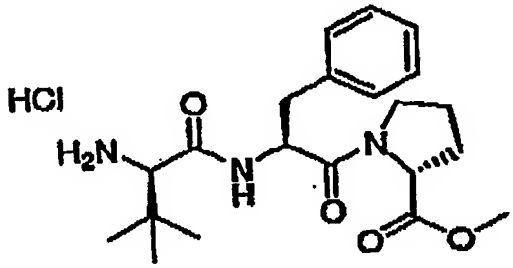
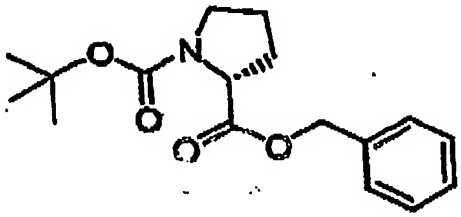
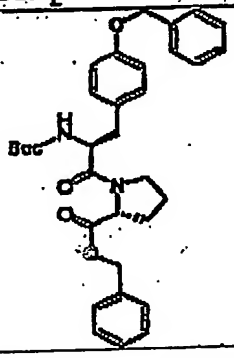
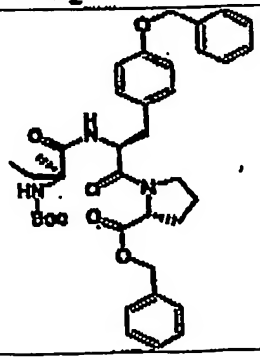
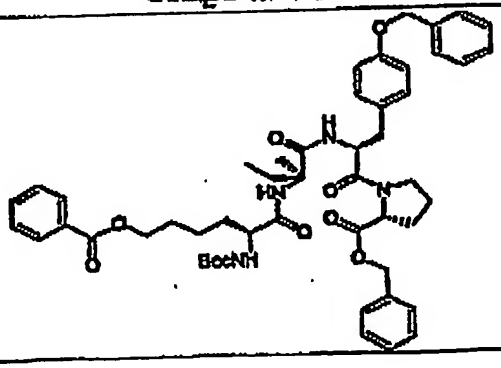
Compound i	Compound j
	
Compound k	**Compound l**
	
Compound A1-1	**Compound A1-2**
	
Compound A1-3	**Compound A1-4**
	

Table 2-3

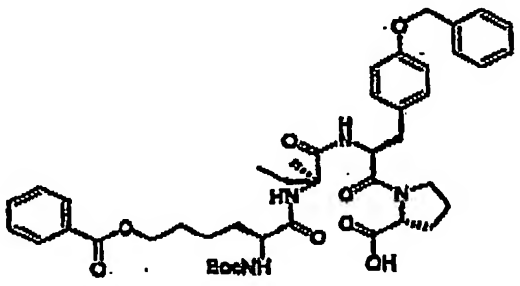
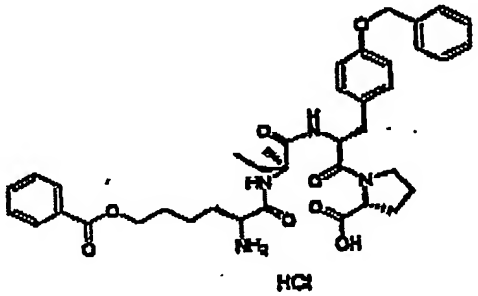
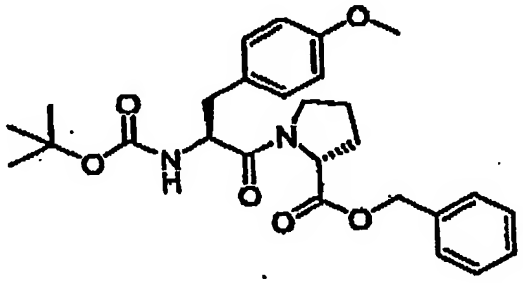
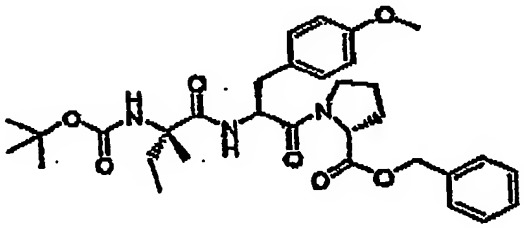
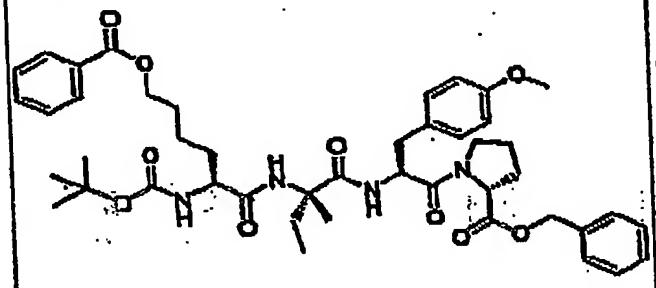
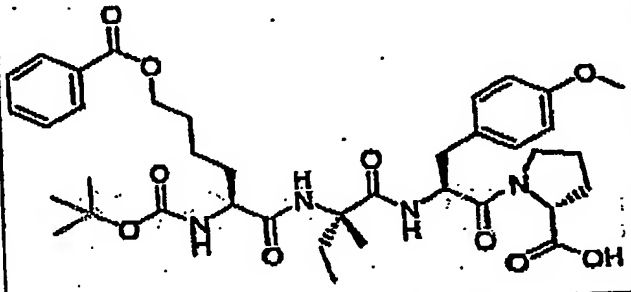
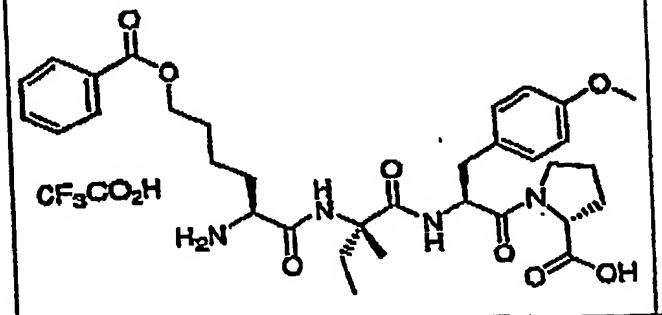
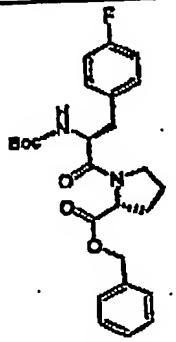
Compound A1-5	Compound A1-6
	
Compound A2-2	**Compound A2-3**
	
Compound A2-4	**Compound A2-5**
	
Compound A2-6	**Compound A3-2**
	

Table 2-4

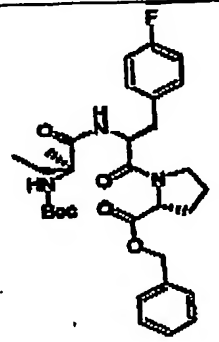
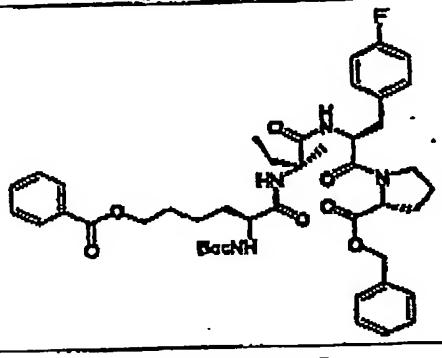
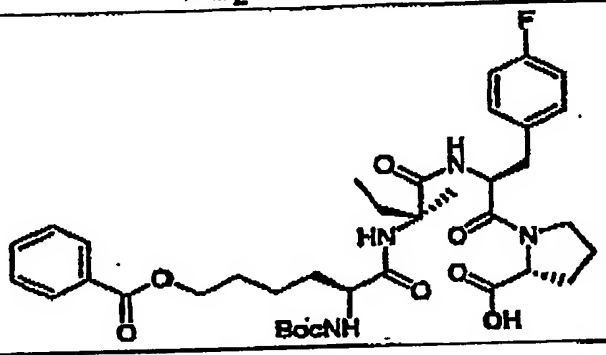
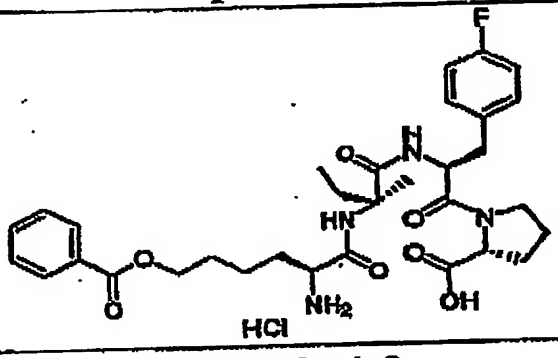
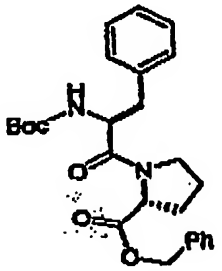
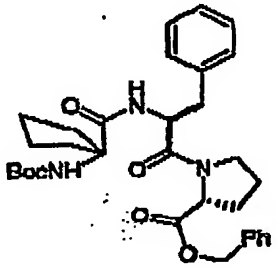
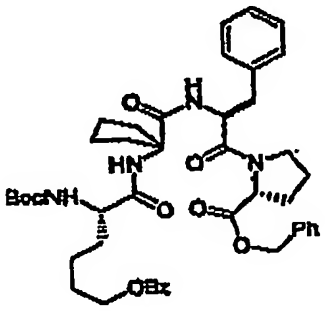
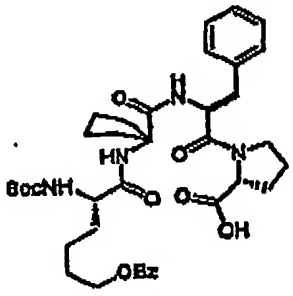
Compound A3-3	Compound A3-4
	
Compound A3-5	**Compound 3-6**
	
Compound A4-2	**Compound A4-3**
	
Compound A4-4	**Compound A4-5**
	

Table 2-5

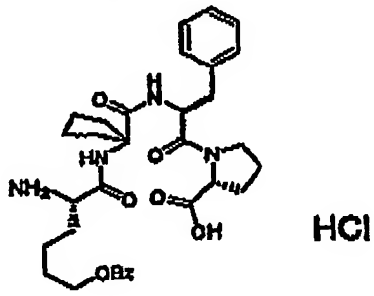
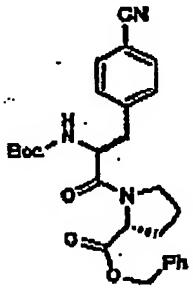
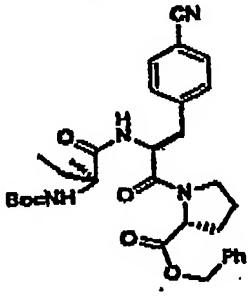
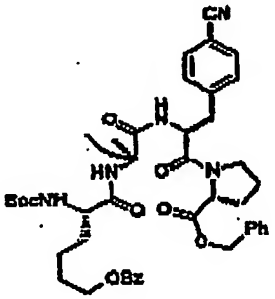
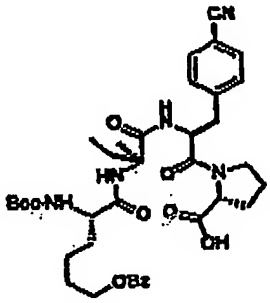
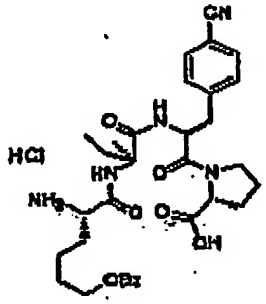
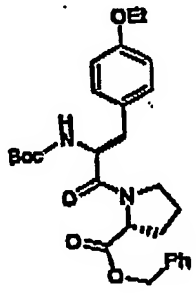
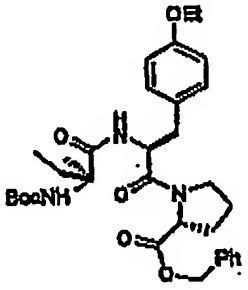
Compound A4-6	Compound A5-2
	
Compound A5-3	**Compound A5-4**
	
Compound A5-5	**Compound A5-6**
	
Compound A6-2	**Compound A6-3**
	

Table 2-6

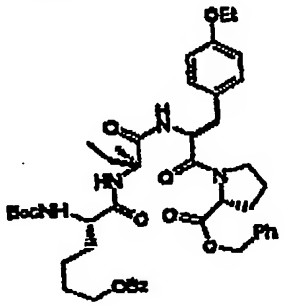
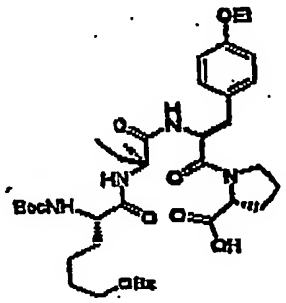
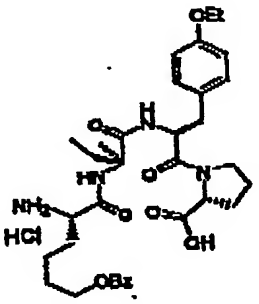
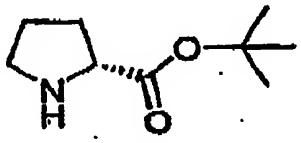
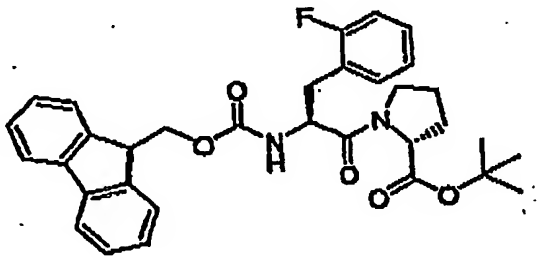
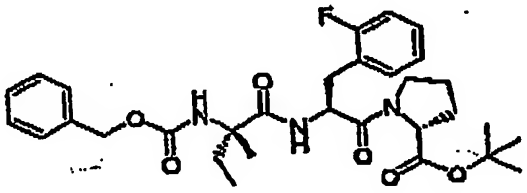
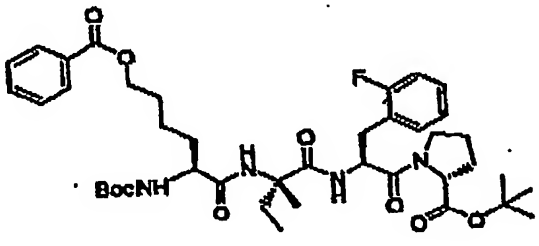
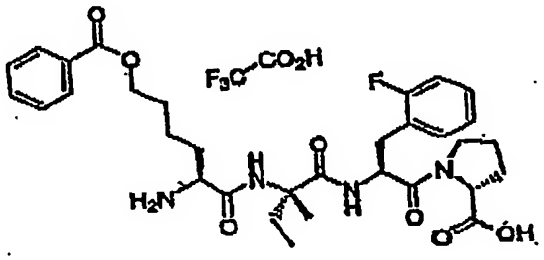
Compound A6-4	Compound A6-5
	
Compound A6-6	**Compound A7-1**
	
Compound A7-2	**Compound A7-3**
	
Compound A7-4	**Compound A7-6**
	

Table 2-7

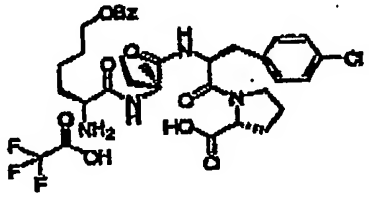
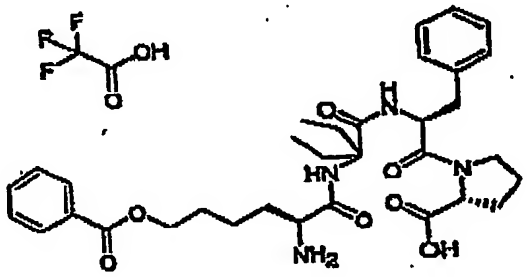
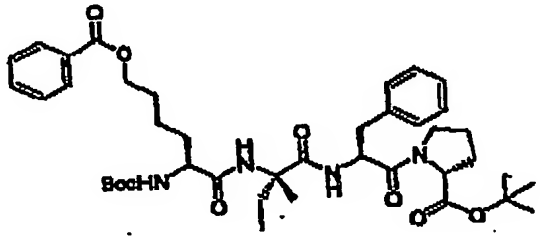
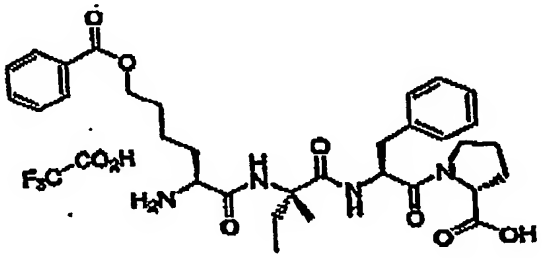
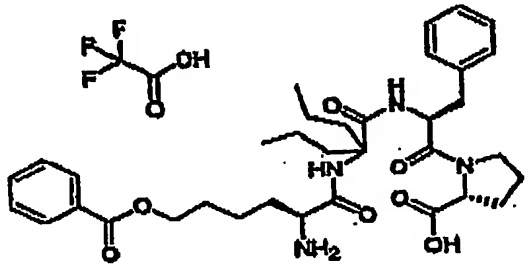
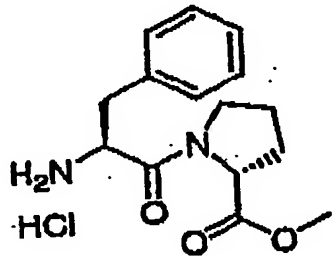
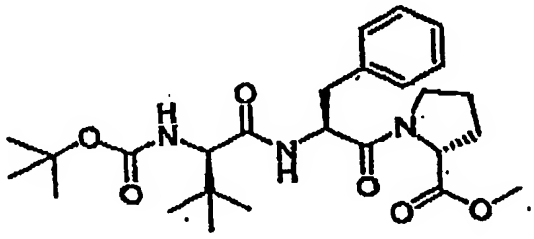
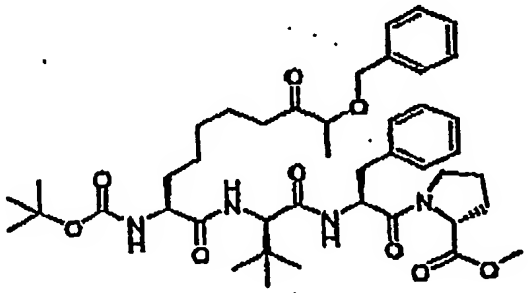
Compound A8-6	Compound A9-6
	
Compound A10-4	**Compound A10-6**
	
Compound A11-6	**Compound A12-2**
	
Compound A12-3	**Compound A12-4**
	

Table 2-8

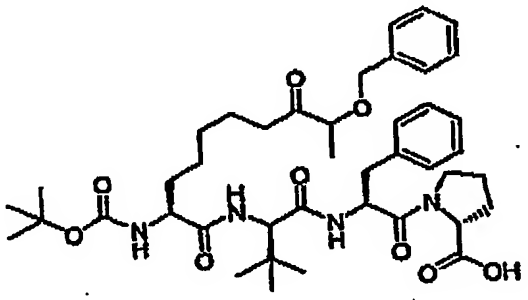
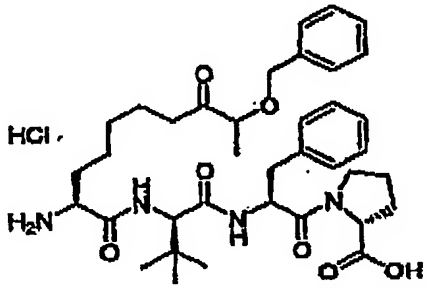
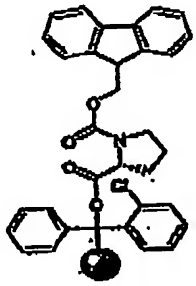
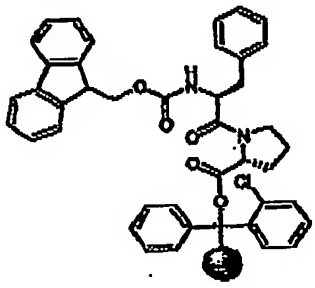
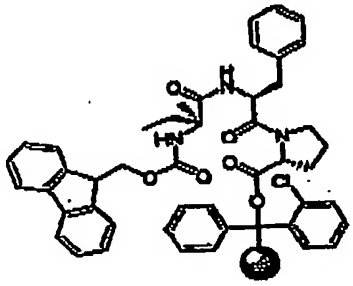
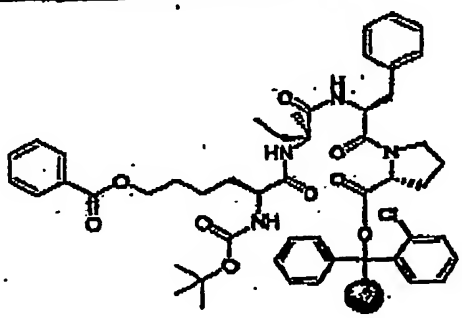
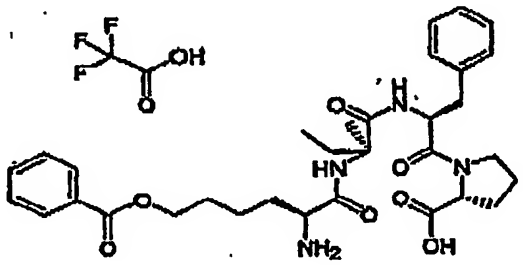
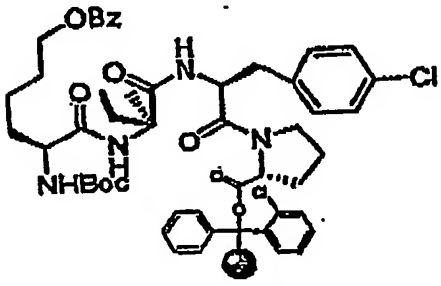
Compound A12-5	Compound A12-6
	
Compound B1-1	**Compound B1-2**
	
Compound B1-3	**Compound B1-4**
	
Compound B1-5	**Compound B2-4**
	

Table 2-9

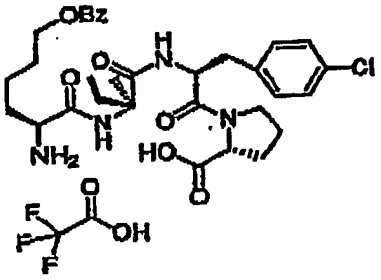
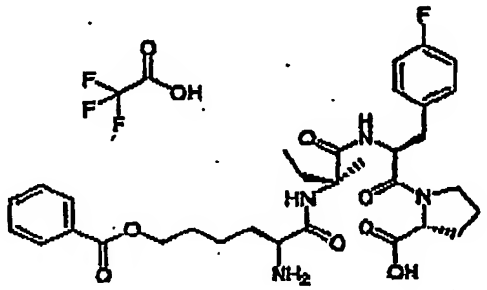
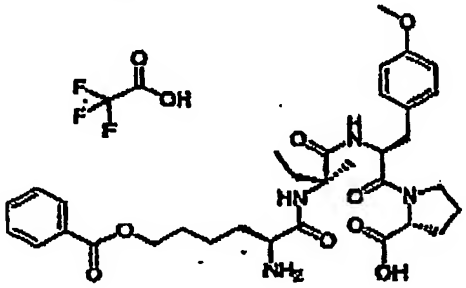
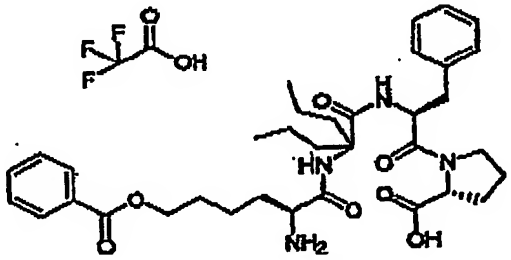
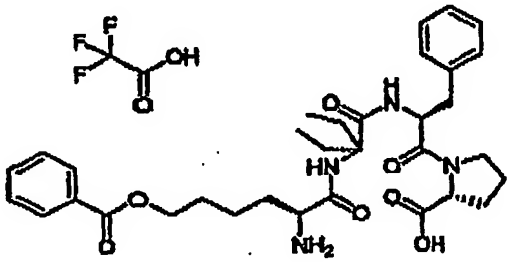
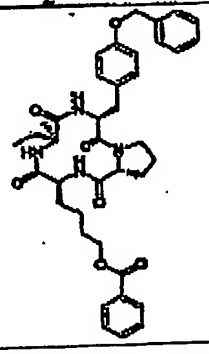
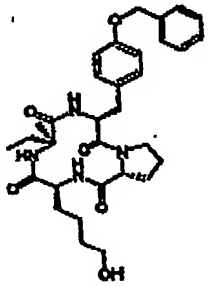
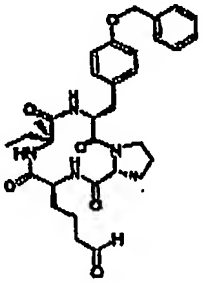
Compound B2-5	Compound B3-5
	
Compound B4-5	**Compound B5-5**
	
Compound B6-5	**Compound C1-1**
	
Compound C1-2	**Compound C1-3**
	

Table 2-10

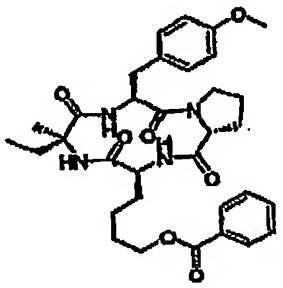
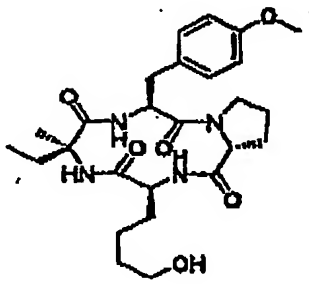
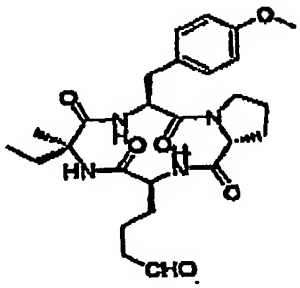
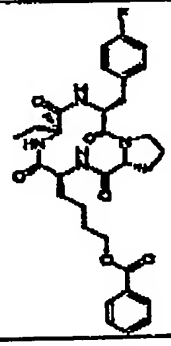
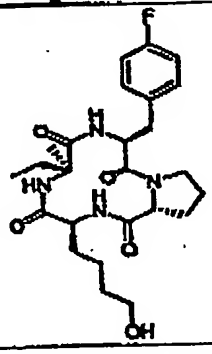
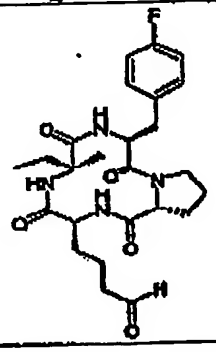
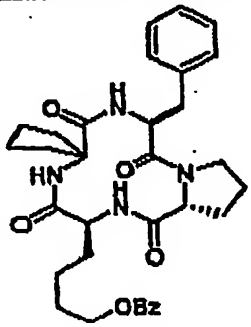
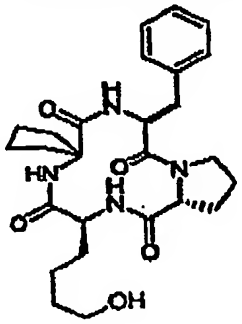
Compound C2-1	Compound C2-2
	
Compound C2-3	**Compound C3-1**
	
Compound C3-2	**Compound C3-3**
	
Compound C4-1	**Compound C4-2**
	

Table 2-11

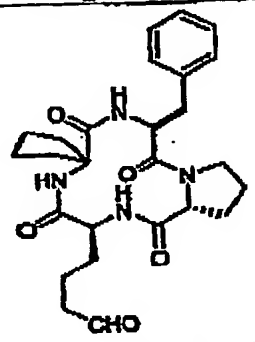
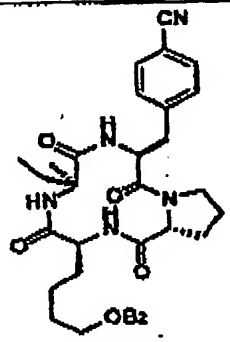
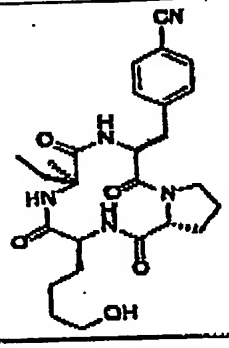
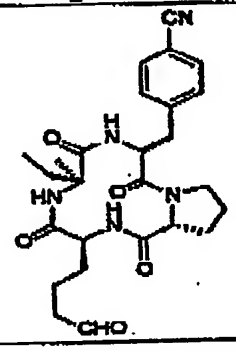
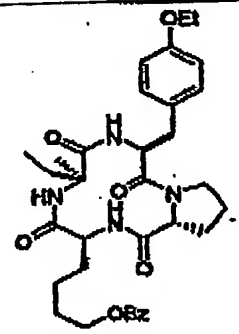
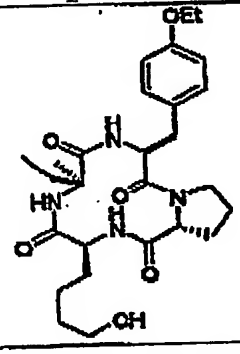
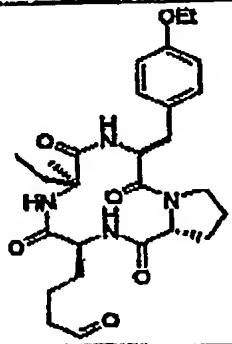
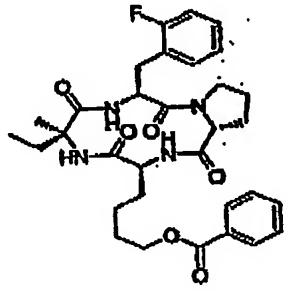
Compound C4-3	Compound C5-1
	
Compound C5-2	**Compound C5-3**
	
Compound C6-1	**Compound C6-2**
	
Compound C6-3	**Compound C7-1**
	

Table 2-12

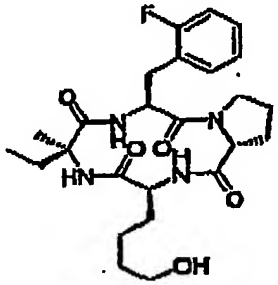
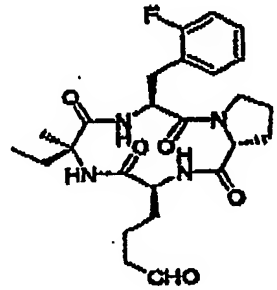
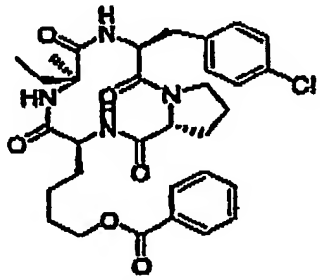
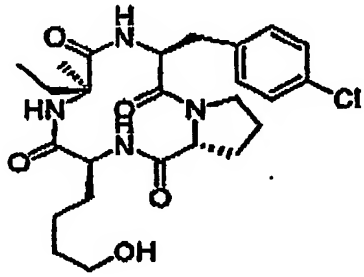
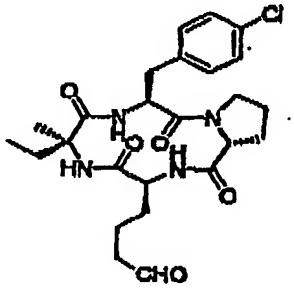
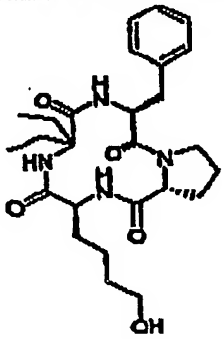
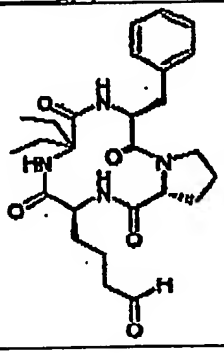
Compound C7-2	Compound C7-3
	
Compound C8-1	**Compound C8-2**
	
Compound C8-3	**Compound C9-1**
	
Compound C9-2	**Compound C9-3**
	

Table 2-13

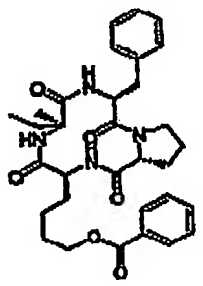
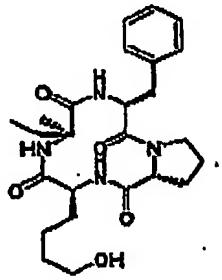
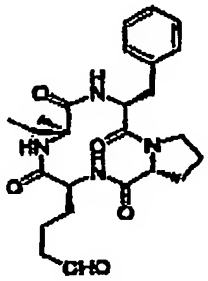
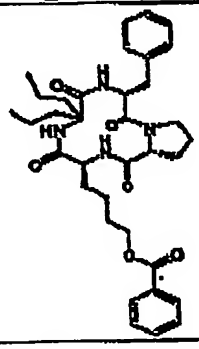
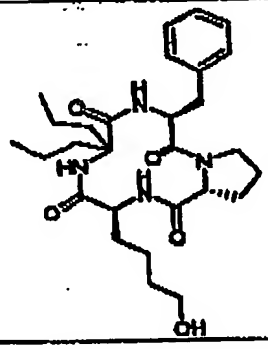
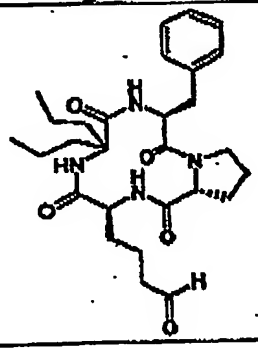
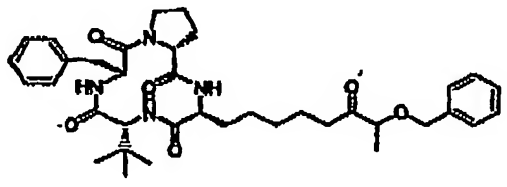
Compound C10-1	Compound C10-2
	
Compound C10-3	**Compound C11-1**
	
Compound C11-2	**Compound C11-3**
	
Compound C12-1	
	

Table 2-14

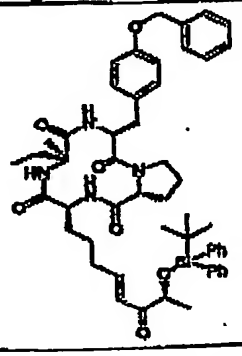
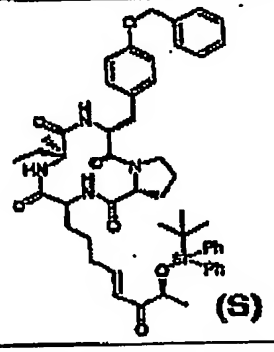
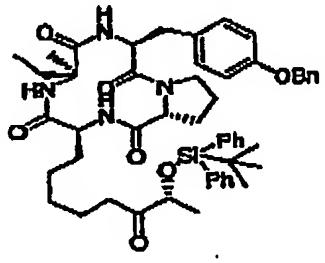
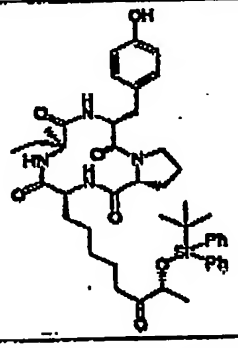
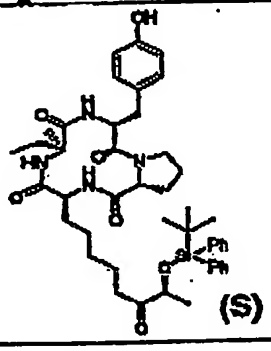
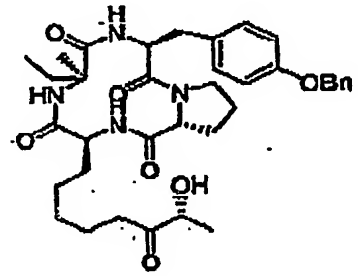
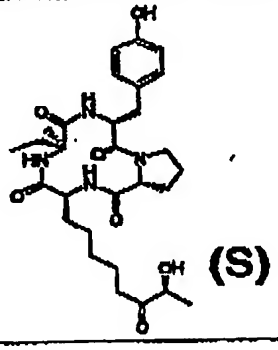
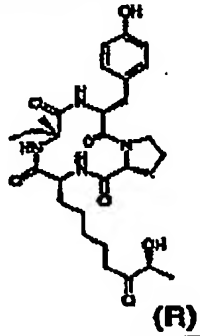
Compound E1-1(1)	Compound E1-1(2)
	
Compound E1-2(1)	**Compound E1-2(2)**
	
Compound E1-2(3)	**Compound E1-3(1)**
	
Compound E1-3(2)	**Compound E1-3(3)**
	

Table 2-15

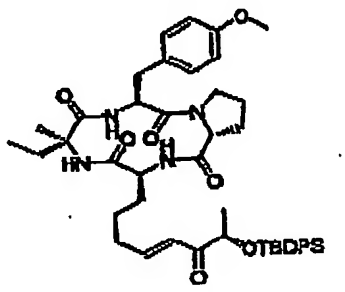
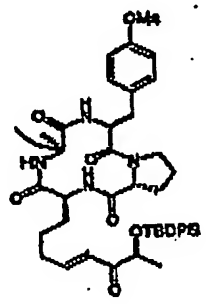
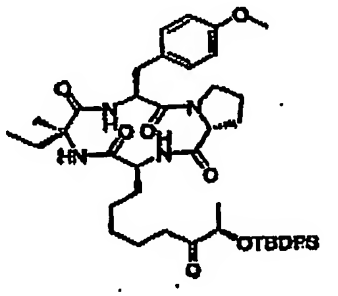
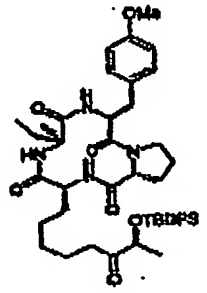
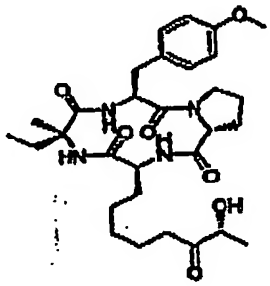
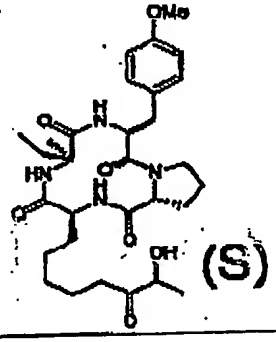
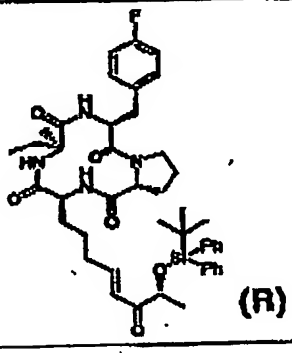
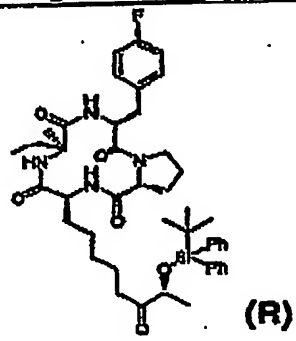
Compound E2-1(1)	Compound E2-1(2)
	
Compound E2-2(1)	**Compound E2-2(2)**
	
Compound E2-3(1)	**Compound E2-3(2)**
	
Compound E3-1	**Compound E3-2**
	

Table 2-16

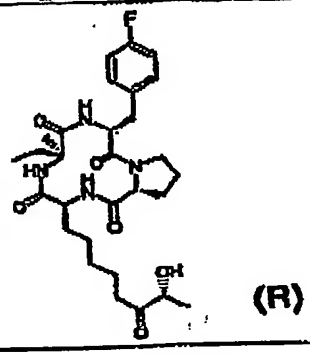
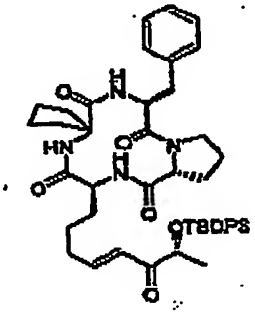
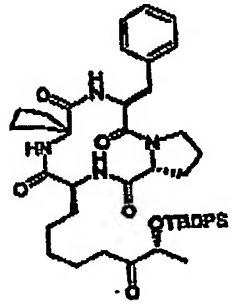
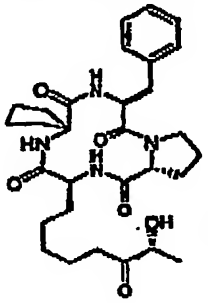
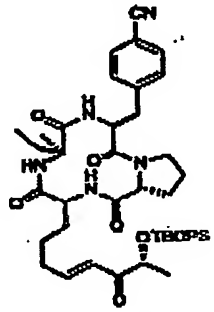
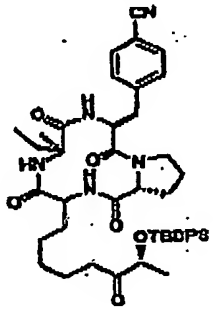
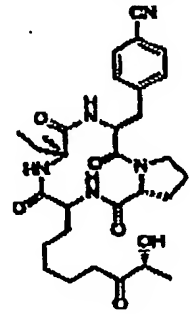
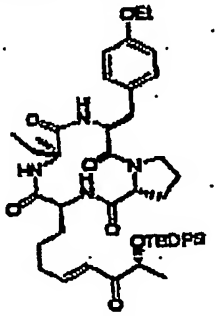
Compound E3-3	Compound E4-1
 (R)	
Compound E4-2	**Compound E4-3**
	 (R)
Compound E5-1	**Compound E5-2**
	
Compound E5-3	**Compound E6-1**
	

Table 2-17

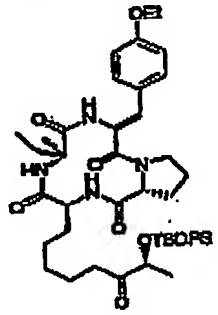
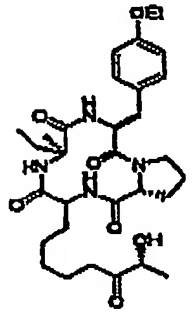
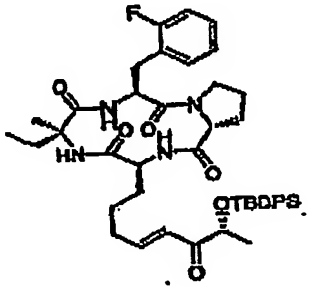
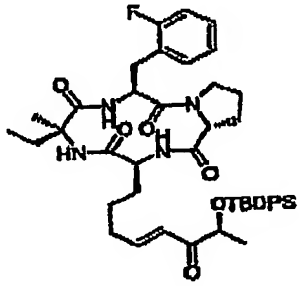
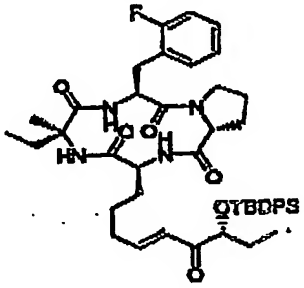
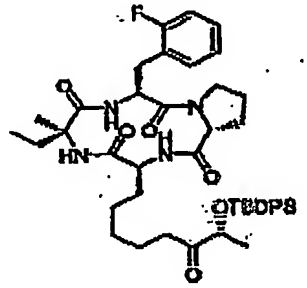
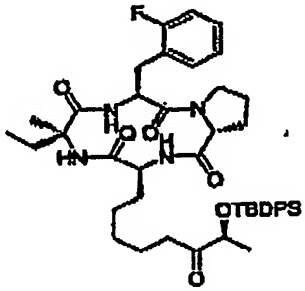
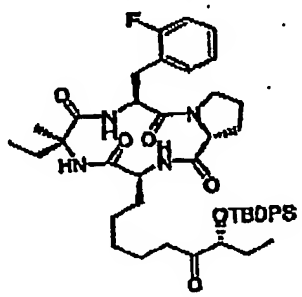
Compound E6-2	Compound E6-3
	
Compound E7-1(1)	**Compound E7-1(2)**
	
Compound E7-1(3)	**Compound E7-2(1)**
	
Compound E7-2(2)	**Compound E7-2(3)**
	

Table 2-18

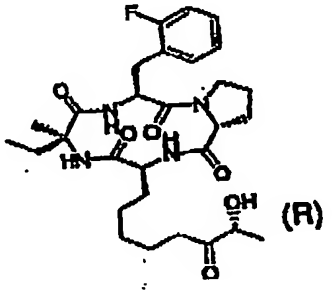
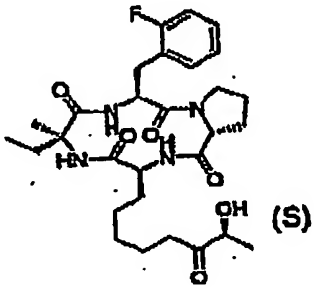
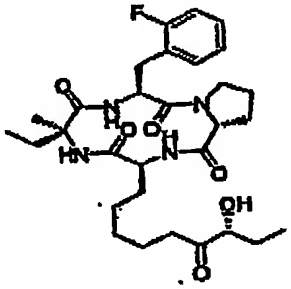
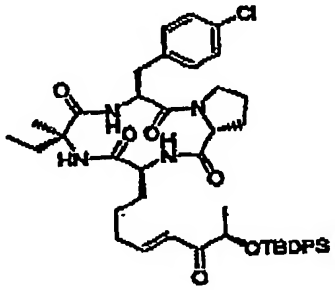
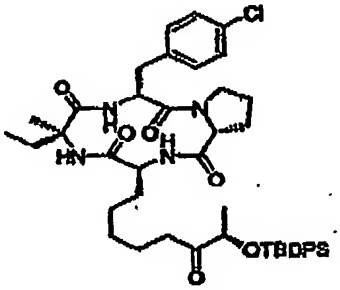
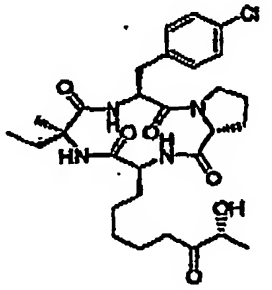
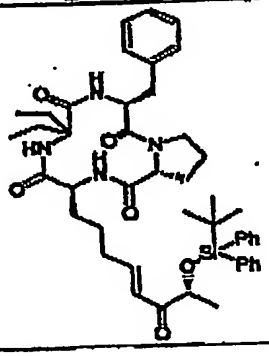
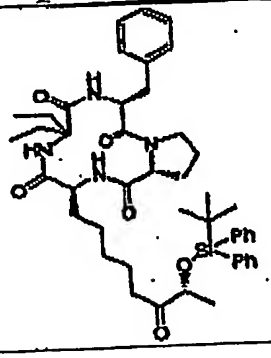
Compound E7-3(1)	Compound E7-3(2)
 (R)	 (S)
Compound E7-3(3)	**Compound E8-1**
	
Compound E8-2	**Compound E8-3**
	
Compound E9-1	**Compound E9-2**
	

Table 2-19

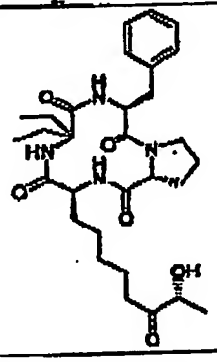
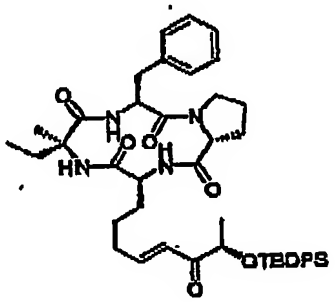
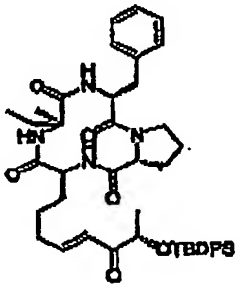
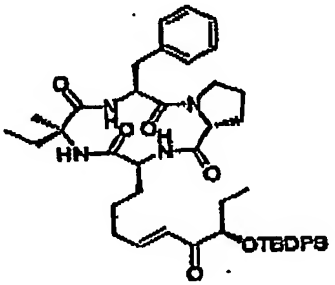
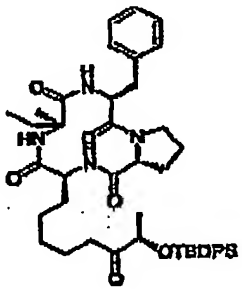
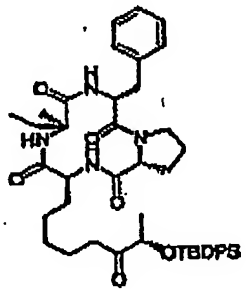
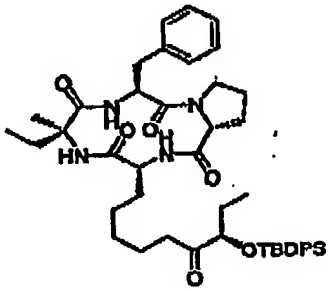
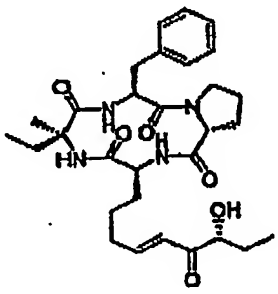
Compound E9-3	Compound E10-1(1)
	
Compound E10-1(2)	**Compound E10-1(3)**
	
Compound E10-2(1)	**Compound E10-2(2)**
	
Compound E10-2(3)	**Compound E10-3(1)**
	

Table 2-20

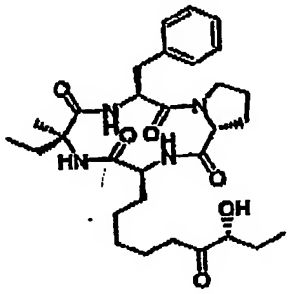
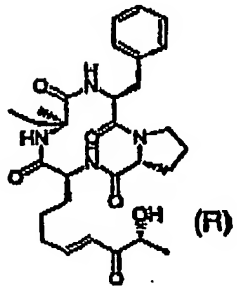
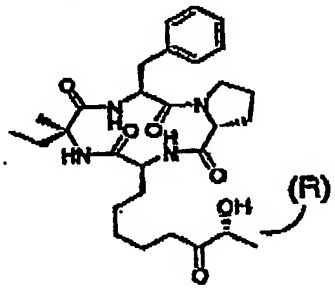
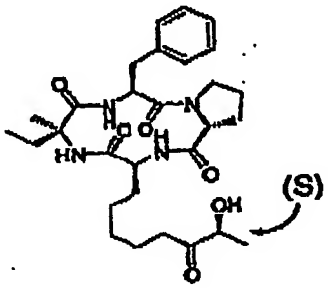
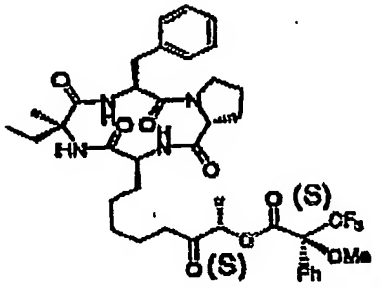
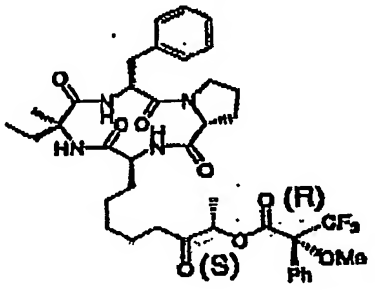
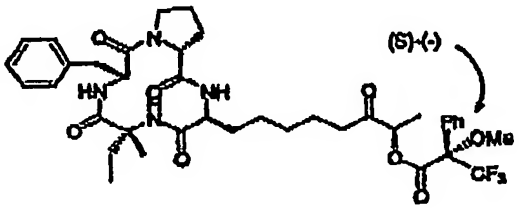
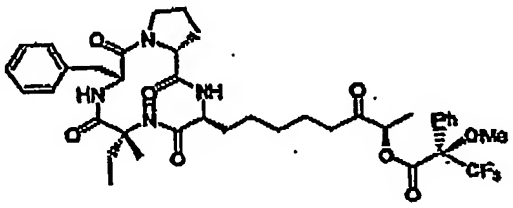
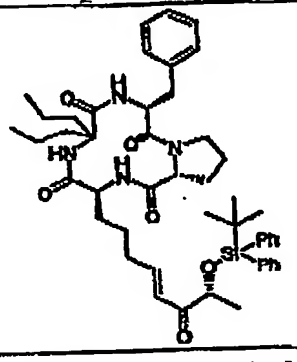
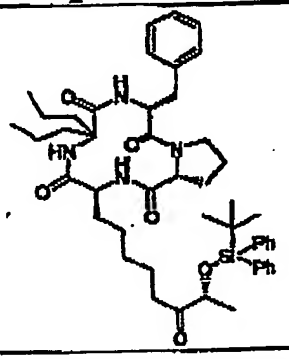
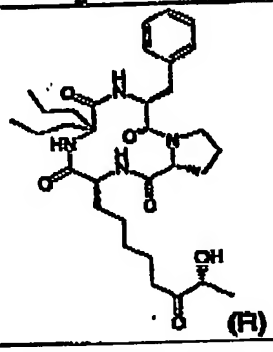
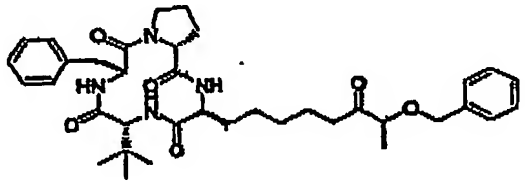
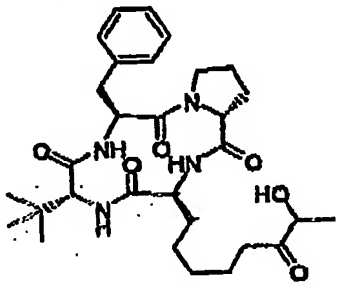
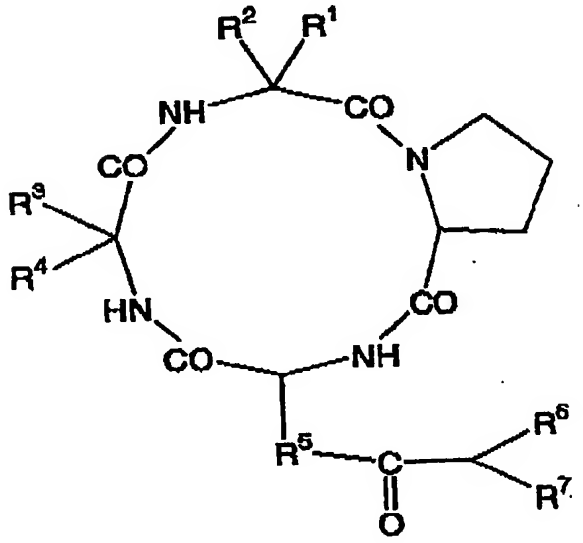
Compound E10-3(2)	Compound E10-3(3)
	
Compound E10-3(4)	**Compound E10-3(5)**
	
Compound E10-4(1)	**Compound E10-4(2)**
	
Compound E10-4(3)	**Compound E10-4(4)**
	

Table 2-21

Compound E11-1	Compound E11-2
	
Compound E11-3	**Compound E12-2**
	
Compound E12-3	
	

CLAIMS

1. A cyclic tetrapeptide compound of the formula (I):



(I)

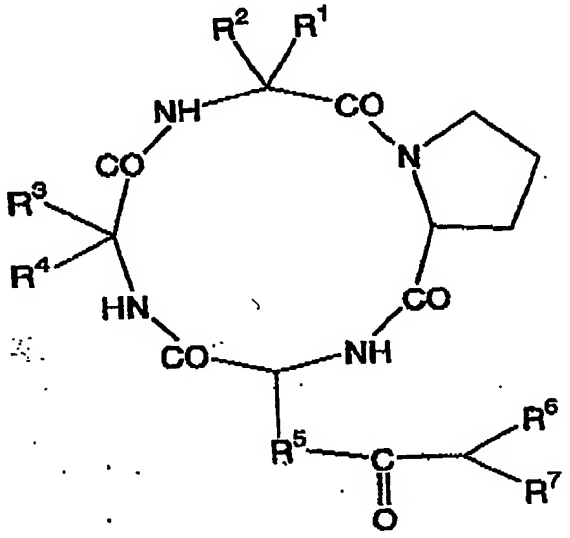
wherein
R^1 is hydrogen,
R^2 is ar(lower)alkyl optionally substituted with one or more suitable substituent(s),
R^3 and R^4 are each hydrogen or lower alkyl, or
R^3 and R^4 are linked together to form lower alkylene,
R^5 is lower alkylene or lower alkenylene,
R^6 is hydroxy or protected hydroxy, and
R^7 is lower alkyl,
providing that,
when R^3 is methyl, R^4 is methyl or ethyl, R^5 is pentylene, R^6 is hydroxy and R^7 is methyl, then R^2 is phenyl(lower)alkyl substituted with one or more suitable substituent(s),
or a salt thereof.

2. The cyclic tetrapeptide compound of claim 1, wherein
R^2 is phenyl(lower)alkyl optionally substituted with one or more suitable substituent(s) selected from the group consisting of lower alkoxy, ar(lower)alkyloxy, cyano, hydroxy and halogen,
R^3 and R^4 are each lower alkyl, and
R^5 is lower alkylene.

3. A pharmaceutical composition containing the cyclic tetrapeptide compound of claim 1 or 2 as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

4. The cyclic tetrapeptide compound of claim 1 or 2 for use as a medicament.

5. A histone deacetylase inhibitor comprising a cyclic tetrapeptide compound of the formula (I):



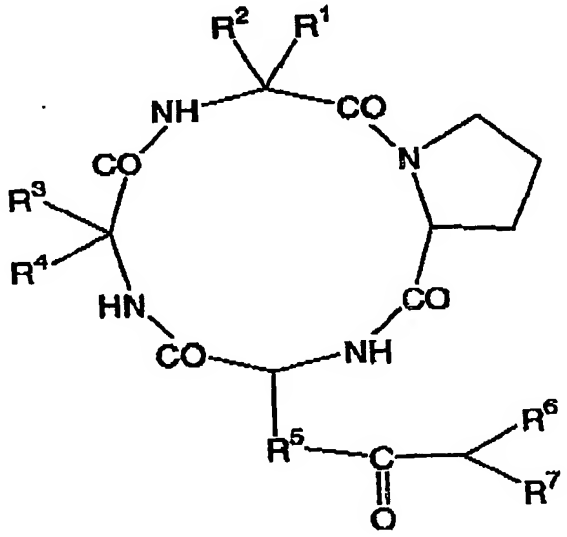
(I)

wherein
R^1 is hydrogen,
R^2 is ar(lower)alkyl optionally substituted with one or more suitable substituent(s),
R^3 and R^4 are each hydrogen or lower alkyl, or
R^3 and R^4 are linked together to form lower alkylene,
R^5 is lower alkylene or lower alkenylene,
R^6 is hydroxy or protected hydroxy, and
R^7 is lower alkyl,
providing that,
when R^3 is methyl, R^4 is methyl or ethyl, R^5 is pentylene, R^6 is hydroxy and R^7 is methyl, then R^2 is phenyl(lower)alkyl substituted with one or more suitable substituent(s),
or a salt thereof.

6. A method for inhibiting histone deacetylase, comprising using a cyclic tetrapeptide compound (I) of claim 5.

7. A use of a cyclic tetrapeptide compound (I) of claim 5 for the manufacture of a medicament for inhibiting histone deacetylase.

8. A pharmaceutical composition for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises, as an active ingredient, a cyclic tetrapeptide compound of the formula (I):



(I)

wherein
R^1 is hydrogen,
R^2 is ar(lower)alkyl optionally substituted with one or more suitable substituent(s),
R^3 and R^4 are each hydrogen or lower alkyl, or
R^3 and R^4 are linked together to form lower alkylene,
R^5 is lower alkylene or lower alkenylene,
R^6 is hydroxy or protected hydroxy, and
R^7 is lower alkyl,
providing that,
when R^3 is methyl, R^4 is methyl or ethyl, R^5 is pentylene, R^6 is hydroxy and R^7 is methyl, then R^2 is phenyl(lower)alkyl substituted with one or more suitable substituent(s),

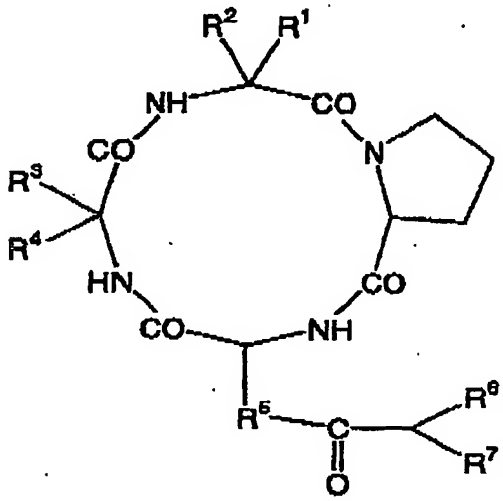
or a salt thereof.

9. A method for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises administering a cyclic tetrapeptide compound (I) of claim 8 to a human being or an animal.

10. A use of a cyclic tetrapeptide compound (I) of claim 8 for the manufacture of a medicament for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors.

ABSTRACT

A cyclic tetrapeptide compound of the formula (I):



(I)

wherein

R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in the description, or a salt thereof;

a pharmaceutical composition containing the compound (I) as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient;

the compound (I) for use as a medicament;

a use of the compound (I) for manufacture of a medicament for inhibiting histone deacetylase;

a use of the compound (I) for manufacture of a medicament for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infections, organ transplant rejections, autoimmune diseases, or tumors;

a use of histone deacetylase inhibitors as an immunosuppressant or an antitumor agent; and

a use of histone deacetylase inhibitors for manufacture of a medicament for treating or preventing organ transplant rejections, autoimmune diseases, protozoal infections or tumors are described.